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(54) Title: GIBBON APE LEUKEMIA VIRUS-BASED RETROVIRAL VECTORS		
(57) Abstract <p>The present invention provides replication-defective hybrid retroviral vectors comprising GaLV components and methods for preparing and using such vectors. The vectors comprise an envelope component, a core component and a defective genome, at least one of which is derived from GaLV. The vectors can comprise the minimal <i>cis</i> acting sequences from GaLV that allow packaging of the defective genome in a hybrid virion.</p>		

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Gibbon Ape Leukemia Virus-based Retroviral Vectors

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BACKGROUND OF THE INVENTION

The present invention relates generally to retroviral vectors. In particular, the invention relates to retroviral vectors comprising nucleic acid sequences from
10 Gibbon Ape Leukemia Virus.

Considerable effort is now being directed to introducing engineered genes into mammalian cells for a variety of applications including gene therapy and the production of transgenic animals. Such strategies are
15 dependent upon the development of effective means for safe delivery of genes to appropriate target cells and tissues.

Retroviral vectors are particularly useful for directing desired polynucleotides to the appropriate cells and integration of the polynucleotides in the host cell genome.
20 For example, the majority of the approved gene transfer trials in the United States rely on replication-defective retroviral vectors harboring a therapeutic polynucleotide sequence as part of the retroviral genome (Miller et al. *Mol. Cell. Biol.* 10:4239 (1990); Kolberg R J. *NIH Res.* 4:43 (1992); Cornetta et
25 al. *Hum. Gene Ther.* 2:215 (1991)). As is known in the art, the major advantages of retroviral vectors for gene therapy are the high efficiency of gene transfer into certain types of replicating cells, the precise integration of the transferred genes into cellular DNA, and the lack of further spread of the
30 sequences after gene transfer.

Unfortunately, many human cells are not efficiently infected by prior art retroviral vectors. Reduced susceptibility to retroviral infection is most likely due to inefficiencies in one of three stages of viral replication:
35 1) binding to retroviral receptors on the cell surface and early viral entry, 2) late entry and transport of the viral genome to the cell nucleus and integration of the viral genome into the target cell DNA, and 3) expression of the viral

genome. These three stages are governed, respectively, by the viral envelope proteins, the viral core proteins, and the viral genome. All three of these components must function efficiently in a target cell to achieve optimal therapeutic gene delivery.

Gibbon Ape Leukemia Virus (GaLV) uses a cell surface internalization receptor that is different from those of the available retroviral vectors and thus allows infection of cells and tissues normally resistant to retroviral infection. The human receptor for GaLV has recently been cloned and shows a wide cell type and species distribution. Johann et al., *J. Virol.* 66:1635-1640 (1992). Indeed, GaLV can infect many mammalian species with the notable exception of mouse cells. The same receptor is used by simian sarcoma associated virus (SSAV), a strain of GaLV. Sommerfelt et al., *Virol.* 176:58-59 (1990).

The construction of hybrid virions having GaLV envelope proteins has been demonstrated. For instance, Wilson et al., *J. Virol.* 63:2374-2378 (1989), describe preparation of infectious hybrid virions with GaLV and human T-cell leukemia virus retroviral env glycoproteins and the gag and pol proteins of the Moloney murine leukemia virus (MoMLV). In addition, Miller et al., *J. Virol.* 65:2220-2224 (1991), describe construction of hybrid packaging cell lines that express GaLV envelope and MoMLV gag-pol proteins.

Existent retroviral vectors capable of infecting human cells all contain core and genome components that derive from MoMLV. For human cells which are resistant to efficient infection by such vectors at any of the three stages noted above, new vectors comprising improved envelope, core or regulatory sequences must be designed. Thus, there is a need to design retroviral vectors components which can be used to introduce genes into human cells not efficiently infected by the currently utilized retroviral vectors. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

The present invention provides recombinant DNA constructs comprising a defective viral genome having a polynucleotide sequence of interest and a GaLV component. For instance, the GaLV component may be a GaLV packaging site which directs packaging of the defective viral genome in an infectious, replication-defective virion. The packaging site typically consists of between about 150 base pairs and about 1500 base pairs and includes a sequence extending from about position 200 to about position 1290 of the sequence shown in Figure 1.

The construct may further comprise GaLV regulatory sequences which direct expression of the polynucleotide of interest. Typically, the regulatory sequences comprise a GaLV (e.g., GaLV SEATO or GaLV SF) 5' or 3' LTR promoter.

The invention also relates to mammalian cells comprising the defective viral genome described above. The mammalian cells may be packaging cells, in which case the cells will also contain retroviral *gag*, *pol* and *env* genes. These genes may be derived from MoMLV, GaLV SF or GaLV SEATO. Packaging cells conveniently used in the invention include PG13 and PA317.

The invention further provides isolated hybrid virions comprising GaLV (e.g., SF or SEATO) envelope proteins and an RNA genome comprising a polynucleotide sequence of interest and a GaLV component. The virions typically contain GaLV core proteins. MoMLV core proteins can also be used.

The invention also provides isolated recombinant DNA constructs comprising polynucleotide sequences which encode an infectious GaLV virion capable of infecting a mammalian cell and producing functional viral progeny. The infectious clones typically comprise about 97% GaLV SEATO sequences and 3% GaLV SF sequences.

Also disclosed are methods of introducing a polynucleotide of interest into human cells using the hybrid virions described above. The methods are preferably used as part of a gene therapy protocol for treating a human patient.

DEFINITIONS

A "hybrid virion" is a virion comprising genome, core, and envelope components derived from more than one virus. The term specifically includes "pseudovirions" which historically have been defined as containing the genome from one virus and the structural proteins from another.

A "packaging cell" is a genetically constructed mammalian tissue culture cell that produces the necessary viral structural proteins required for packaging. The cells are incapable of producing infectious virions until a defective genome is introduced into the cells. The genetic material for the viral structural proteins is not transferred with the virions produced by the cells, hence the virus cannot replicate.

A "replication-defective" virion or retroviral vector is one produced by a packaging cell as defined above. Such a virion infects a target cell but is incapable of producing progeny virions which can infect other cells.

Two polynucleotides or polypeptides are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman *Adv. Appl. Math.* 2: 482 (1981), by the homology alignment algorithm of Needleman and Wunsch *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson and Lipman *Proc. Natl. Acad. Sci. (U.S.A.)* 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection. These references are incorporated herein by reference.

The percentage of sequence identity between two sequences is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the

number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity.

5 For instance, a preferred method for comparing sequences uses the GAP program based on the algorithm of Needleman et al., *supra*. Typically, the default values for all parameters are selected. These are gap weight: 5.0, length weight: 0.30, average match: 1.0, and average mismatch:
10 0.0.

The term "substantial identity" means that a polynucleotide or polypeptide comprises a sequence that has at least 80% sequence identity, preferably 90%, more preferably 95% or more, compared to a reference sequence over a
15 comparison window of about 20 bp to about 2000 bp, typically about 50 to about 1500 bp, usually about 350 bp to about 1200. The values of percent identity are determined using the GAP program, above.

Another indication that nucleotide sequences are
20 substantially identical is if two molecules hybridize to each other under stringent conditions. Stringent conditions are sequence dependent and will be different in different circumstances. Generally, stringent conditions are selected to be about 5° C lower than the thermal melting point (T_m) for
25 the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Typically, stringent conditions will be those in which the salt concentration is about 0.2 molar at pH 7 and
30 the temperature is at least about 60°C.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the complete sequence of the GaLV SEATO genome, as published in Delassus, et al. (1989) *Virology*.
35 173:205-213.

Figures 2A-2F show the construction of the infectious GaLV clone of the invention.

Figure 3 shows packagable defective genomes of the present invention.

Figure 4 shows schematic diagrams of plasmids 395, 558, and 521.

5 Figure 5 shows schematic diagrams of plasmids 395, 559 and 537.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

New hybrid retroviral vectors comprising GaLV
10 components are provided by the present invention. The tissue specificity of the vectors is determined by the viral envelope proteins, the viral core proteins, and the viral genome, at least one of which is derived from GaLV. The vectors can comprise the minimal *cis* acting sequences (packaging signals)
15 from GaLV that allow packaging of a defective genome in a replication-defective hybrid virion. In addition, the LTR of the defective genome can be derived from GaLV. For instance, the 3' LTR region of the hybrid retroviral vector can be selected from various GaLV sequences to provide desired tissue
20 specific expression of the structural genes in the genome.

Replication-defective retroviral vectors are produced when a defective DNA viral genome is introduced into a packaging cell line. The defective genome contains the sequences required for integration into the target cell
25 genome, for packaging of the genome into infectious virions, as well as those viral sequences required for expression of the therapeutic gene or other polynucleotide contained within the defective viral genome. The packaging cells comprise the *gag*, *pol*, and *env* genes which encode the viral core and
30 envelope components. These core and envelope proteins assemble around the defective genome, thus producing retroviral vectors.

A number of standard techniques are used to ensure safety of retroviral vectors. For instance, the defective
35 genome is introduced into the cell separately from the genes encoding the core and envelope components. In this way, recombination between the genome and the core and envelope genes, which would lead to the packaging of complete viral

genomes, is extremely unlikely. The resulting virions should therefore not comprise the *gag*, *pol*, and *env* genes and are thus replication-defective. Homologous recombination, however, between the inserts can lead to the production of infectious virions. Typically, the packaging cells are produced by introducing the *gag*, *pol*, and *env* genes on at least two separate plasmids. This scheme effectively prevents homologous recombination leading to reconstruction of infectious virus because the probability of multiple, independent homologous recombination events occurring is extremely low.

Retroviral vectors can also be designed to prevent synthesis of viral proteins by the integrated defective genome. For instance, if a portion of the *gag* gene is included to increase packaging efficiency, a stop codon can be introduced into the gene to prevent synthesis of *gag* proteins. Miller et al., *BioTechniques* 7:982-988 (1989), which is incorporated herein by reference.

In addition, the cells used to make packaging cells do not possess a cell receptor for GaLV and are thus not infectable by GaLV. Retroviral vector virions having the GaLV envelope therefore cannot reinfect the packaging cells and vector spread in the packaging cells is greatly reduced. Suitable packaging cells also have limited or no endogenous viral sequences. Cell lines for this purpose include the *Mus dunni* tail fibroblast cell line. This strategy decreases the potential for generation of recombinant vectors, which are often transmitted with higher efficiency than the parental vector.

Finally, replication-defective vectors of the invention are particularly safe because GaLV is evolutionarily derived from a xenotropic virus of an asian strain of mouse and does not appear to be closely related to human pathogenic viruses. Thus, in terms of containment, GaLV-based, replication-defective hybrid virions are as safe as prior art murine retroviral vectors and provide a safe vehicle for delivery of genes for human gene therapy.

The packaging cell lines of the invention can be used to provide infectious replication-defective hybrid virions for use in gene transfer in humans, hamsters, cows, cats, dogs, monkeys, chimpanzees, macaques, primates, and other species whose cells have host cell receptors for GaLV envelope proteins.

Generally, the nomenclature used hereafter and the laboratory procedures in cell culture, molecular genetics, and nucleic acid chemistry described below are those well known and commonly employed in the art. Standard techniques are used for recombinant nucleic acid methods, polynucleotide synthesis, and cell culture. Generally, enzymatic reactions, oligonucleotide synthesis, oligonucleotide modification, and purification steps are performed according to the manufacturers' specifications. The techniques and procedures are generally performed according to conventional methods in the art and various general references which are provided throughout this document. A basic text disclosing the general methods of use in this invention is Sambrook et al., *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Publish., Cold Spring Harbor, NY 2nd ed. (1989), which is incorporated herein by reference.

A first step in the synthesis of retroviral vectors of the invention is obtaining an infectious GaLV DNA clone. Proviral DNA from at least three GaLV strains (GaLV SF, GaLV SEATO, and SSAV) has been cloned. A GaLV SF clone including both ends of the GaLV SF genome and the envelope gene but not an intact region of the genome encoding the core proteins is reported by Scott et al. *Proc. Natl. Acad. Sci. USA* 78:4213-4217 (1981). A partial clone containing the envelope and part of the genome but not the region encoding core proteins of SSAV is described by Gelman et al. *Proc. Natl. Acad. Sci. USA* 78:3373-3377(1981). Finally, Gelman et al. *J. Virol.* 44:269-275 (1982) disclose a partial clone of a third GaLV strain, SEATO, containing all but 350 bases of the core region of GaLV. This clone has been sequenced in its entirety by Delassus et al. *Virol.* 173:205-213 (1989) (see Figure 1). The deleted 350 bases were also sequenced but from a PCR fragment

generated from viral RNA expressed in a GaLV SF infected cell line. The sequence of an integrated form of a GaLV SEATO genome is also shown in Seq ID No. 1. All of the above references are incorporated herein by reference.

5 Example 1 describes the construction of an infectious GaLV clone comprising sequences from GaLV SEATO and GaLV SF. This construction can be used to prepare a number of retroviral vectors, as described in detail below.

Packaging Cells

10 Packaging cells for use in the present invention may be made from any animal cell, such as CHO cells, NIH 3T3, mink lung cells, D17 canine cells, and MDBK cells. One or both of the core and envelope components can be encoded by GaLV genes. The core and envelope components, however, need not be derived
15 from the same GaLV strain. Indeed, in some embodiments, the core components may be derived from a different species (e.g. MoMLV). For example, the PG13 murine packaging cell line produces virion particles having MoMLV core and GaLV envelope particles (see Miller, et al. (1991) *J. Virol.* 65:2220-2224).

20 To prepare a packaging cell line, an infectious clone of a desired retrovirus (e.g., GaLV SEATO) in which the packaging site (ψ) has been deleted is constructed. Cells comprising this construct will express all GaLV structural proteins but the introduced DNA will be incapable of being
25 packaged. Alternatively, packaging cell lines can be produced by transforming a cell line with one or more expression plasmids encoding the appropriate core and envelope proteins. In these cells, the *gag*, *pol*, and *env* genes can be derived from the same or different retroviruses.

30 Although certain cells may express the receptor for a retroviral vector, the cells may not be efficiently infected because of a loss of optimum fit between the receptor and the envelope proteins. For example, altered glycosylation patterns may inhibit retroviral infection (Wilson et al., *J.*
35 *Virol.* 65:5975-5982 (1991), which is incorporated herein by reference). In addition, retroviruses in the same receptor class can exhibit different host ranges due to single amino acid differences in target cell receptors.

In light of these considerations, it may be necessary to modify the envelope proteins of the hybrid virions to adjust the host range. The proteins may be modified to either allow infection of cells previously resistant to infection or to prevent infection of non-target cells.

One strategy for modifying envelope proteins is the use of an *in vitro* selection scheme. In this approach, an infectious clone of the retrovirus along with a selectable marker gene is introduced into target cells that are resistant to infection. Those cells which have been infected by retroviruses comprising mutations allowing infection of the cells are then identified by standard reverse transcriptase assays of the culture supernatant. The *env* gene of the adapted retrovirus is cloned and sequenced and used to construct new retroviral vectors capable of efficiently infecting the target cell. This strategy is particularly useful in isolating variants capable of infecting a number of human cells currently resistant to GaLV infection such as tumor infiltrating lymphocytes, bone marrow cells, stem cells, and hepatocytes.

Alternatively, if the gene encoding the cell receptor has been cloned, the gene can be inserted in a cell line which does not normally produce the receptor. Variant retroviruses capable of binding the receptor can then be identified in the same manner as described above. For instance, the human GaLV cell surface receptor has been cloned and sequenced. U.S. Patent No. 5,151,361, and Johann et al., *J. Virol.* 66:1635-1640 (1992), which are incorporated herein by reference. Thus, this gene can be used to identify new retroviral vectors expressing modified envelope proteins.

A third alternative to modifying the host range of a retrovirus vector is by directly modifying the envelope proteins. Modifications of the sequences encoding the polypeptides may be readily accomplished by a variety of well-known techniques, such as site-directed mutagenesis (see, e.g., Gillman and Smith, *Gene* 8:81-97, (1979) and Roberts, S. et al., *Nature* 328:731-734, (1987), which are incorporated

herein by reference). The effect of the modifications are evaluated by screening for the ability of the engineered virions to infect a target cell.

In addition, specific polynucleotide sequences encoding desired polypeptides can be fused to the env gene using methods known to those skilled in the art. Gene fusions comprising sequences encoding antibodies, SCF, IL-6 somatostatin and the like can thus be used as a targeting means. The fused gene can be inserted into an appropriate plasmid for transformation into the packaging cells.

In addition, the envelope protein can be modified for example, by introducing point mutations in the protein to yield moieties for coupling by organic chemical means (e.g., insertion of a cysteine residue to give a sulfhydryl group). Cell-specific targeting moieties can be coupled with glutaraldehyde, periodate, or maleimide compounds, or by other means known to those skilled in the art. Such couplings may also be made directly to wild-type or unmodified envelope proteins where coupling can be to a carbohydrate moiety, a sulfhydryl group, an amino group, or other group which may be available for binding.

A number of packaging cell lines suitable for the present invention are also available in the prior art. These lines include Crip and GPE-Am. Preferred existing cell lines include PA317 (ATCC CRL 9078) which expresses MoMLV core and envelope proteins and PG13 (ATCC CRL 10,683) which produces virions having MoMLV core and GaLV envelope components. (See Miller et al. J. Virol. 65:2220-2224 (1991), which is incorporated herein by reference.) The PG13 packaging cell line can be used in conjunction with the 521 plasmid and the 537 plasmid, both of which contain 5' MoMLV LTR and packaging signal sequences (see Example 3, herein).

Defective Genomes

The other component of retroviral vectors is a packagable defective genome comprising a polynucleotide sequence, typically a structural gene, of interest. The defective genomes of the invention include a GaLV component which include minimal GaLV nucleotide sequences must be

present in the defective genome itself for the genome to integrate in the target cell genome and be packaged in infectious virions (i.e. the sequences are required in *cis*). Thus, the GalV component of the defective genomes of the invention may include the packaging site, ψ , and/or the long terminal repeated sequences (LTRs). The LTRs are positioned at either end of the proviral DNA and contain regulatory sequences (e.g., promoters, enhancers and polyadenylation sequences) which direct expression of the genes within the proviral DNA. The polynucleotide sequences of the GalV component may be identical to sequences as shown, for instance, in SEQ ID. No 1, or may be substantially identical to that sequence as defined, above.

Typically, the proviral regulatory sequences drive expression of the inserted gene. In those embodiments where two inserted genes are included (e.g., a marker gene and the gene of interest) it is frequently desirable to include a virus internal ribosome entry site (IRES) to increase efficiency of expression (Ghattas et al., *Mol. Cell. Biol.* 11:5848-5859 (1991), which is incorporated herein by reference).

The promoter operably linked to the gene of interest may be constitutive, cell type-specific, stage-specific, and/or modulatable (e.g., by hormones such as glucocorticoids). Suitable promoters for the invention include those derived from genes such as early SV40, CMV major late, adenovirus immediate early, histone H4, β -actin, MMTV, and HSV-TIC.

Enhancers increase the rate of transcription from promoters, act on *cis*-linked promoters at great distances, are orientation independent, and can be located both upstream, (5'), and downstream, (3'), from the transcription unit. Enhancers inducible by hormones and metal ions and found only in specific tissues have been described. Proteins synthesized only in one tissue type, for example, actin and myosin in muscle, are frequently regulated by tissue specific enhancers. For tissue specific expression of the introduced genes of interest used in the retroviral vectors of the present

invention, tissue-specific enhancers are of particular interest.

A repetitive 45 base pair enhancer element in the U3 region of the GaLV LTR is important for tissue specific expression of the introduced genes. This enhancer region is present only once in the 3' LTR of GaLV SF but is present 3 times in the 3' LTR of GaLV SEATO. (See Quinn et al., *Mol. Cell. Biol.* 7:2735-2744, which is incorporated herein by reference). The sequence of the 3' LTR of GaLV SEATO with 3 repeats of the 45 bp enhancer region is shown in Seq. ID No.2.

Thus, the origin of the 3' GaLV LTR region (from GaLV SEATO or GaLV SF) in a retroviral vector can influence the expression of the introduced gene in different tissues (see Example 4, herein).

To ensure efficient expression, 3' polyadenylation regions must be present to provide for proper maturation of the mRNA transcripts. The native 3'-untranslated region of the gene of interest is preferably used, but the polyadenylation signal from, for example, SV40, particularly including a splice site, which provides for more efficient expression, could also be used. Alternatively, the 3'-untranslated region derived from a gene highly expressed in a particular cell type could be fused with the gene of interest.

The retroviral vectors of the invention also contain GaLV-based regulatory elements that can direct expression of genes contained within the genome in a tissue/cell specific manner. In general, the GaLV regulatory elements are more efficient than the MoMLV elements in expressing genes in human cells. In addition, the regulatory sequences from different GaLV strains have different cell and tissue specificities. For instance, GaLV SF regulatory genes function efficiently in primate lymphoid cells (e.g., UCD 144) and GaLV SEATO regulatory genes function efficiently in human myeloid cells (e.g., HL60 cells), while MoMLV regulatory genes do not. Thus, tissue specificity of the vectors of the invention can be modified by selecting the appropriate GaLV strain. Tissue specificity of the regulatory genes from various GaLV strains

is determined using routine screening techniques well-known to those of skill in the art.

The 5' and 3' LTRs of one retrovirus or GaLV strain may be also used in a defective genome derived from another.

5 For instance, the 3' LTR from SSAV can be substituted for the 3' LTR of an infectious clone of another GaLV strain. Since the U3 region of the 3' LTR is the template for the synthesis of the U3 region in both 5' and 3' LTRs of the progeny virus, the 3' LTR will be duplicated and transferred to the 5' LTR in
10 the host cell. In this way optimal expression of the gene of interest in the target cell can be achieved.

In addition, in order to increase efficiency of packaging, the 5'LTR from one virus (e.g., MoMLV) can be used in combination with the 3' LTR of a second (e.g., GaLV). If the constructs
15 comprise a MoMLV 5'LTR and a GaLV 3'LTR, they are efficiently expressed in murine packaging cells (e.g., PG13) but result in proviral DNA comprising promoter sequences from GaLV which function more efficiently in human cells. These constructs are efficiently packaged in packaging cells such as PG13
20 because the 5' MoMLV LTR drives gene transcription in the packaging cells. However, when the packaged retroviral vector is infected into an appropriate target cell, the 3' GaLV promoter drives gene transcription (see Example 3, herein). Examples of retroviral vectors with MoMLV 5' LTR's and
25 packaging signals and 3'GaLV LTR's include plasmids 521 and 537, described in Example 3, herein. This type of retroviral vector has the advantages of both efficient packaging in cell lines such as PG13 and higher expression in various target cells (see Example 4, herein).

30 The cis-acting packaging sequences used in the defective viral genomes may be derived from GaLV SEATO. The minimal sequences required for efficient packaging of a GaLV-based defective genome are described herein. In particular, as shown in detail below, the first 910 to 1290 nucleotides
35 from the 5' end of the GaLV SEATO genome can direct packaging of a defective genome by PG13 and PA317 cells. This result also shows that the sequences required for efficient packaging from GaLV are recognized by MoMLV core proteins. Thus, hybrid

retroviral vectors comprising both GaLV and MoMLV components can be conveniently constructed.

5 The GaLV SEATO sequences required for packaging of the defective genomes include the 5' LTR and extend to about position 1290 of the GaLV genome illustrated in Figure 1. The sequences required for packaging also include the packaging site, ψ , which is typically defined negatively as a sequence which, when deleted from a viral genome, prevents efficient packaging of the genome. In the GaLV SEATO genome, ψ is
10 located downstream of the 5' LTR beginning at about position 200. The site usually comprises at least about 350 bp, preferably between about 500 bp and about 1500 bp, more preferably about 700 to about 1200 bp. One of skill will recognize that minor modifications to the packaging sequence shown in Figure 1 will not substantially affect the ability of
15 the sequence to direct packaging. Thus, the term "GaLV packaging site" as used herein refers to GaLV DNA sequences, or RNA sequences transcribed from them which are capable of directing packaging when present in *cis* in a GaLV genome or defective genome. The term "GaLV SEATO packaging sites"
20 refers to those DNA or RNA sequences substantially identical (as determined above) to the disclosed sequences and which are functional in the defective GALV genomes of the present invention.

25 The retroviral vectors of the invention are suitable for delivering a variety of polynucleotides to cells, including transgenes for augmenting or replacing endogenous genes in gene therapy or for the production of transgenic animals. Antisense polynucleotides can be used to control
30 expression of target endogenous genes such as oncogenes. In addition, genes encoding toxins can be targeted for delivery to cancer cells. Other suitable sequences include those encoding growth substances to promote immune responses to cancers or infections, soluble factors to modulate receptor
35 activity, and the like. The inserted polynucleotide of interest should be less than about 10 kb, preferably between about 7 and 8 kb.

In certain embodiments, homologous targeting constructs are used to replace an endogenous target gene. Methods and materials for preparing such constructs are known by those of skill in the art and are described in various references. See, e.g., Thomas et al., *Cell* 51:503 (1987) and Capecchi, *Science* 244:1288 (1989), which are incorporated herein by reference.

Homologous targeting constructs have at least one region having a sequence that substantially corresponds to, or is substantially complementary to, a predetermined endogenous target gene sequence (e.g., an exon sequence, an enhancer, a promoter, an intronic sequence, or a flanking sequence of the target gene). Such a homology region serves as a template for homologous pairing and recombination with substantially identical endogenous gene sequence(s). In the targeting of transgenes, such homology regions typically flank the replacement region, which is a region of the targeting transgene that is to undergo replacement with the targeted endogenous gene sequence. Thus, a segment of the targeting transgene flanked by homology regions can replace a segment of the endogenous gene sequence by double crossover homologous recombination.

In addition, the constructs for both homologous targeting and random integration will comprise a selectable marker gene to allow selection of cells. Frequently, multiple selectable marker genes are incorporated, such as in positive-negative selection constructs for homologous gene targeting.

A selectable marker gene expression cassette typically comprises a promoter which is operational in the targeted host cell linked to a structural sequence that encodes a protein that confers a selectable phenotype on the targeted host cell, and a polyadenylation signal. A promoter included in an expression cassette may be constitutive, cell type-specific, stage-specific, and/or modulatable (e.g., by hormones such as glucocorticoids; MMTV promoter), but is expressed prior to and/or during selection.

When the selectable marker is contained in a homologous targeting construct, homologous recombination at

the targeted endogenous site(s) can be chosen to place the selectable marker structural sequence downstream of a functional endogenous promoter, and it may be possible for the targeting construct replacement region to comprise only a structural sequence encoding the selectable marker, and rely upon an endogenous promoter to drive transcription.

Similarly, an endogenous enhancer located near a targeted endogenous site may be relied on to enhance transcription of selectable marker gene sequences in enhancerless constructs.

Suitable selectable marker genes include, for example: *gpt* (encoding xanthine-guanine phosphoribosyltransferase), which can be selected for with mycophenolic acid; *neo* (encoding neomycin phosphotransferase), which can be selected for with G418, and DFHR (encoding dihydrofolate reductase), which can be selected for with methotrexate. Other suitable selectable markers will be apparent to those in the art.

Selection for correctly targeted recombinant cells will generally employ at least positive selection, wherein a selectable marker gene expression cassette encodes and expresses a functional protein (e.g., *neo* or *gpt*) that confers a selectable phenotype to targeted cells harboring the endogenously integrated expression cassette, so that, by addition of a selection agent (e.g., G418, puromycin, or mycophenolic acid) such targeted cells have a growth or survival advantage over cells which do not have an integrated expression cassette.

Cells harboring the transgene of interest either randomly integrated or integrated by homologous recombination may be further identified using techniques well known in the art. For instance, the cells can be screened using Southern blotting or the polymerase chain reaction (PCR). If targeted integration is being screened, the oligonucleotide probes or PCR primers should bracket recombination junctions that are formed upon transgene integration at the desired homologous site.

Gene Therapy

The retroviral vectors of the invention are particularly suitable for delivering polynucleotides to cells for gene therapy of a number of diseases. Current strategies for gene therapy are reviewed in Friedmann, *Science* 244:1275 (1989), which is incorporated herein by reference.

Delivery of the polynucleotide of interest may be accomplished *in vivo* by administration of the vectors to an individual patient, typically by systemic administration (e.g., intravenous, intraperitoneal, intramuscular, subdermal, or intracranial infusion). Alternatively, the vectors may be used to deliver polynucleotides to cells *ex vivo* such as cells explanted from an individual patient (e.g., tumor-infiltrating lymphocytes, bone marrow aspirates, tissue biopsy) or universal donor hematopoietic stem cells, followed by reimplantation of the cells into a patient, usually after selection for cells which have incorporated the polynucleotide.

The vectors may be used for gene therapy to treat congenital genetic diseases, acquired genetic diseases (e.g., cancer), viral diseases (e.g., AIDS, mononucleosis, herpesvirus infection, cytomegalovirus infection, papillomavirus infection) or to modify the genome of selected types of cells of a patient for any therapeutic benefit. Treatable disorders include hemophilia, thalassemias, ADA deficiency, familial hypercholesterolemia, inherited emphysema, cystic fibrosis, Duchenne's muscular dystrophy, lysosomal storage diseases, Gaucher's disease, and chronic granulomatous disease.

The vectors of the invention can be used to introduce polynucleotides into a variety of cells and tissues including myeloid cells, bone marrow cells, lymphocytes, hepatocytes, fibroblasts, lung cells, and muscle cells. For example, polynucleotides conferring resistance to a chemotherapeutic agent may be transferred to non-neoplastic cells, especially hematopoietic cells. Alternatively, polynucleotides comprising a toxin gene (e.g., ricin or diphtheria toxin) expression cassette or a negative selectable marker gene expression cassette may be selectively inserted

into neoplastic cells. Expression of the toxin gene or negative selection gene (followed by negative selection) selectively kills target cells. Polynucleotides which are not cytotoxic but which reverse or suppress the neoplastic phenotype (e.g. antisense inhibition of oncogene expression) also may be used to treat cancer, as well. Other uses include the introduction of immunomodifiers into bone marrow cells to treat cancers.

Transgenic Animals

As noted above, the vectors of the present invention are particularly useful for gene targeting mediated by homologous recombination between a targeting polynucleotide construct and a homologous chromosomal sequence. In addition to gene therapy, such strategies are also useful for the production of transgenic animals.

The ability to introduce new genes into the germ line of an animal has been extremely valuable for basic understanding of gene expression. The improvement of desired traits in agricultural or domesticated animals is also possible using these techniques. For example, potential new traits that may be introduced include sterility in meat producing strains of cattle, or fertility and milk production in dairy cows. Other commercially desirable properties include hardiness and rapid weight gain in livestock, or "show qualities" in domestic animals such as dogs and cats. For a review of the genetic engineering of livestock see, Pursel et al, *Science* 244:1281 (1989), which is incorporated herein by reference.

Typically, embryonic stem (ES) cells are used as the transgene recipients. Cells containing the newly engineered gene are injected into a host blastocyst, which is reimplanted into a recipient female. Some of these embryos develop into chimeric animals that possess germ cells partially derived from the mutant cell line. By breeding the chimeric animals it is possible to obtain a new line containing the introduced gene.

The following examples are provided by way of illustration, not limitation.

Example 1

Construction of GaLV infectious clone comprising GaLV SEATO and GaLV SF sequences.

5 To prepare the GaLV infectious clone, a missing fragment of about 250 kb from the *pol* gene of a GaLV SEATO clone was replaced with the corresponding sequence from GaLV SF. The following steps correspond to the numbered steps illustrated in Figures 2A-2F.

10 The steps illustrated in Figure 2A show repair of *pol* gene of GaLV-SEATO.

- 1 The approximately 8.5 kb permuted GaLV-SEATO provirus (pGAS-2 Hd1) from pGAS-2 (Gelman et al., 1982, *supra*) was isolated by HindIII digestion and DEAE-cellulose membrane interception in an agarose gel. An approximately 250 bp GaLV-SF *pol* gene fragment of pGV-3 corresponding to the missing *pol* fragment of PGAS-2 was isolated by HindIII digestion and DEAE-cellulose membrane interception in an agarose gel.
- 2 The two DNA species were ligated at low concentration to favor circularization over multimer formation.
- 3 After ligated material was precipitated, Sal I restriction was used to linearize the construct.
- 4 The construct was ligated into Sal I-restricted and phosphatased pVZ-1 vector.
- 5 DH5 α F' cells were transformed.
6. Transformants were screened by alkaline lysis, plasmid mini-preps, and sequencing with "GVGAS 10" primer to check number and orientation of GaLV-SF *pol* fragment inserts within GaLV-SEATO sequence. A clone with correct construction was named intermediate Clone 66.

35 Figure 2B shows change of GaLV-SEATO insert orientation.

7 The permuted proviral Clone 66 insert was
isolated by Sal I digestion and DEAE-cellulose
membrane interception on an agarose gel.

8 The insert was re-ligated back into pVZ-1 Sal
5 I-cut and phosphatased vector to obtain
opposite orientation. The opposite orientation
clone was named intermediate Clone 120.

Figures 2C and 2D illustrate the intermediate Clone
66 and the unidirectional decrease in insert length using
10 Exonucleases III and VII.

9 Intra-insert distances were estimated by known
sequence and accurate restriction mapping. The
goal was to decrease the 8.5 kb insert by 5.4
15 kb, stopping at a point just 3' of the LTR-LTR
junction, leaving one LTR intact. The size of
resulting clone (vector + insert) was ~ 6 kb.

10 Not I restriction of Clone 66 and Clone 120 was
used to check for absence of intra-insert
sites. They were found to be absent. Clone 66
20 was linearized with Not I in the multiple
cloning site.

11 The Not I termini were filled in with cold
dCTP[α S] and dGTP[α S] and DNA polymerase I
(Klenow). α -thiodeoxyribonucleotides were used
25 to block these termini from Exonuclease III
digestion.

12 Clone 66 and Clone 120 were restricted with Xba
I to check for absence of intra-insert sites.
Clone 66 was restricted with Xba I in the
30 multiple cloning site generating 5' overhang
cohesive termini.

13 Precisely timed Exonuclease III digestion
destroyed the Xba I site but the Sal I site at
5' insert end was left intact, and incomplete
35 Not I site was resistant to attack by
Exonuclease III.

14 Digestion with Exonuclease VII was used to
remove remaining single strand.

15 The "ragged ends" were filled in with DNA
polymerase (Klenow) and cold deoxynucleotide
triphosphates.

16 The blunt ended incomplete Not I site was
5 ligated to insert sequence.

17 DH5 α F' cells were transformed.

18 Transformants were screened by alkaline lysis,
plasmid mini-preps, Sal I linearization and
sequencing to determine (a) extent of insert
10 deletion and (b) quality of incomplete Not I
sites and the true extent of protection given
by α -thiodeoxyribonucleotides from digestion
into the vector by Exonuclease III or VII.

19 Transformants were further screened by Not I
15 digestion, searching for complete Not I site.

20 Clones that linearize with Not I were
linearized to confirm presence of complete Not
I site and accurately determine extent of
insert deletion. One clone with desired
20 digestion to a point just 3' of the LTR-LTR
junction and with a complete Not I site, was
named intermediate Clone 66Exo52.

Figure 2E shows the intermediate Clone 120:
Unidirectional decrease in insert length using Exonucleases
25 III and VII.

21 Intra-insert distance was estimated by known
sequence and accurate restriction mapping. The
goal was to decrease the 8.5 kb insert by 2.6
kb, stopping at a point just 3' of the LTR-LTR
30 junction leaving one LTR intact. Size of
resulting clone was ~ 9 kb.

22 to 32 The steps were preformed as described for steps
10-20. One clone with desired digestion to a
point just 3' of the LTR-LTR junction and with
35 a complete Not I site, was named Intermediate
Clone 120Exo55.

Figure 2F shows coupling of Clone 66Exo52 insert and Clone 120Exo55 insert: separation of LTR's and generation of infectious clone.

- 33 Double digestion of both Clone 66Exo52 and
Clone 120Exo55 with Sal I and Not I was used to
release inserts.
- 34 Inserts were isolated by DEAE cellulose
membrane interception in agarose gels.
- 35 Ligation of Clone 66Exo52 insert, Clone
120Exo55 insert and Not I restricted
pVZ-vector.
- 36 DH5 α F' cells were transformed.
- 37 Screening of transformants by ³²P-labelled
probing of colonies, alkaline lysis plasmid
mini-preps, restriction analysis and sequencing
to search for potential infectious clones with
correct construction.
- 38 Large scale plasmid preparation and restriction
mapping of GaLV-SEATO infectious clone.

The resulting cloned GaLV genome was subsequently
shown to encode infectious GaLV virions.

Example 2

Construction of defective genomes comprising GaLV SF and GaLV SEATO packaging sites.

The steps used to prepare a defective genome
comprising GaLV SEATO sequences from the infectious clone in
Example 1 were as follows.

1. A 1667 bp Not I-Bgl II fragment from the 5' end of the
infectious clone of GaLV SEATO was isolated.
2. A 3116 bp Bam HI-Xba I fragment corresponding to the
Lac Z gene was isolated from the p1203 Lac Z plasmid
(Ghattas et al., supra).

3. A 596 bp Xba I to Hind III fragment corresponding to the ECMV IRES (EMCV internal ribosome entry site) was isolated from pLZIC2 (Ghattas et al., *supra*).
4. A 890 bp Stu I- Sfu I fragment corresponding to the
5 G418 resistance gene was isolated from pRCCMV plasmid (Invitrogen).
5. A 995 bp Stu I-Not I fragment corresponding to the 3' end of the GaLV SEATO infectious clone was isolated.
6. A linearized Not I pGem 13 plasmid (Promega, 3181bp)
10 was isolated.
7. These fragments were ligated together to assemble the pGaLV SEATO 395 plasmid.

Figure 3 (top) shows the resulting defective genome.
15 Figure 3 (middle) shows a defective genome constructed in the same manner but using a Not I-Nco I fragment from the 5' end of the GaLV SEATO genome. Figure 3 (bottom) shows a construct prepared from GaLV SF sequences.

The pGaLV SEATO 395 plasmid was further modified by
20 increasing the length of the 5' putative packaging region by 328 bp in creating the GaLV SEATO 558 construct. Plasmid 558 this represents a modified 395 plasmid which contains an additional 328 nucleotides of 5' GaLV SEATO sequences extending to the Bgl II site at position 1290 of the GaLV
25 genome. (Plasmid 395 extends only to the Nco I site at position 910 of the GaLV genome.) The 558 plasmid construction was made using the 194 GaLV SF plasmid. The GaLV SF 194 plasmid contains a truncated GaLV SF genome cloned into the Promega pSP72 genome at the Eco RI site.

30 The steps in construction of the 558 plasmid are listed below.

1. A Pst I- Bgl II fragment of GaLV SEATO containing the
35 5' GaLV SEATO LTR and the GaLV SEATO packaging site was used to replace the corresponding region of the GaLV SF 194 plasmid partial genome.
2. A Barn HI-Xba I fragment containing the bacterial Lac Z gene but lacking an initiation codon was ligated, in reading frame, to the Bgl II site such that the Lac Z

gene initiated from the GaLV SEATO gag protein translation start codon. Therefore the β -galactosidase protein is a GaLV SEATO gag-Lac Z fusion protein.

5 3. An Xba I to Nsi I fragment containing the EMCV IRES and a G418 gene was ligated to the Xba I site downstream of the Lac Z gene and the Nsi I in the 3' region of the GaLV SF 194 genome.

10 4. The Nsi I- Sma I region at the 3' end of the 194 GaLV SF genome was replaced with a corresponding region of GaLV SEATO, such that the 3' U3 of the LTR contained GaLV SEATO derived sequences in place of the GaLV SF 194 sequences.

15 The schematic diagrams of plasmids 395 and 558 are compared in figure 4 and the nucleotide sequence of plasmid 558 is shown in Seq. ID No. 3.

Example 3

Construction of GALV defective genomes with improved packaging efficiency in murine packaging cell lines that express MoMLV structural proteins

20 In order to improve the efficiency of packaging in murine packaging cell lines such as PG13 and PA317, which express MoMLV structural proteins, we constructed GALV defective genomes that have a MoMLV promoter at the 5' end and a GaLV promoter at the 3' end.

25 Two defective genomes, designated plasmid 521 and plasmid 537, having a MoMLV promoter at the 5' end and a GaLV promoter at the 3' end, were constructed. In order to construct plasmid 521, the 5' end of the 395 plasmid (Sfi I/filled in-Cla I) was replaced with the corresponding
30 fragment of a similar MoMLV-based Lac Z genome (Sst II/filled in to Cla I). In order to construct plasmid 537, the 3' Nsi I- Not I (filled in) fragment of 521 was replaced with Nsi-Bgl II (filled in) fragment of GaLV SF 194.

35 For comparative purposes, a MoMLV defective genome plasmid similar in construction to the 521 plasmid, was prepared by replacing the Spe I- Sph I fragment of pLXSN (which contains the end of the MoMLV packaging region, the SV40 promoter and the 5' part of the G418 gene with the

corresponding region (also an Spe I-Sph fragment) of the 521 genome, thereby replacing the SV40 promoter with an IRES element. This defective genome is designated plasmid 560. Plasmids 521, 537, and 560 are shown schematically in figures 4 and 5. The nucleotide sequence of plasmid 521 is shown in Seq. ID No. 4 and the nucleotide sequence of plasmid 537 is shown in Seq. ID No. 5.

The 521 and 537 plasmid constructs provide a means of optimizing gene expression in the packaging cells while retaining GaLV-driven gene expression in target cells where GaLV promoters function more efficiently than the MoMLV promoter. Because the 521 and 537 constructs have a MoMLV promoter at the 5' end, cells transfected with these constructs (such as packaging cells PA317 and PG 13) have a MoMLV promoter (U3) driving gene transcription. On the other hand, when the genome is reverse transcribed after infection of the target cell, the GaLV U3 promoter in the 3' LTR is duplicated and replaces the MoMLV promoter at the 5' end. This has been demonstrated by sequence analysis of unintegrated vector DNA from 521 target cells (data not shown). The DNA from these cells infected with the 521 construct after packaging in either PG13 or PA317 cells contains a 5' AND 3' GaLV SEATO U3 (data not shown). Therefore the 5' end of the 521 genome switches from a MoMLV U3 to a GaLV SEATO U3 in infected cells, which results in GaLV-driven gene expression in target cells.

Example 4

Effect of the number of 45 bp enhancer elements in the U3 region of the GaLV LTR on efficiency of gene expression in target cells

There are a variable number of repetitive 45 bp enhancer elements in the U3 region of the GaLV LTR. The 558 plasmid and the 521 plasmid U3 regions, derived from GaLV SEATO, each contain 3 repetitive 45 bp enhancer elements, whereas GaLV SF (eg. plasmids 537 and 559) has only one of these elements. The number of repeats may play a restrictive but potentially useful role in governing expression of downstream genes in different target cells. The experimental

data presented below suggests that the number of repetitive 45 bp enhancer elements in the U3 region of the LTR of GaLV can effect the efficiency of tissue/cell specific gene expression.

Following transfection of the 521, 537 or 560 plasmids into the PA317 or PGI3 cell lines, the MoMLV promoters are used to express packagable genomes. For the 521 and 537 plasmids, however, the GaLV promoter is used to express β -galactosidase and G418 resistance in the target cell after infection with the packaged defective genomes. The effect of three repeats of the 45 basepair enhancer region versus only one copy of the enhancer region in the GaLV promoter is shown in the table below. The expression of the G418 indicator gene is measured by titering G418 resistant colonies. The data in the table below demonstrates the effect of varying the number of 45 bp enhancer region repeats on the expression of genes driven by the GaLV LTRs in different cell types (see table).

Table: Efficiency of Gene Expression Directed by Retroviral Vectors in Various Target Cells

genome	537	558	560
packaging cells:	PGI3	PGI3	PGI3
promoter used	GaLV SF	GaLV SEATO	MoMLV
target cells:			
mink fibroblasts	$2 \times 10^{2\#}$	5×10^4	5.0
murine NIH 3T3 cells	5×10^4	5.0	5×10^4
BHK hamster cells	-	0.5×10	-
HaK hamster cells	-	0.5×10^2	-
Bovine MDBK cells	5×10^3	5×10^4	5×10^2
	-*	-*	-*
Human KB cells	5×10^4	5×10^2	5×10
Human HeLA cells	5×10^4	5×10^2	5×10^2
Human 293 cells	5×10	5×10^2	5×10^4
	$5 \times 10^{3*}$	$5 \times 10^*$	$5 \times 10^{3*}$

titer expressed as number of G418 resistant colonies obtained with 1 ml of PGI3 or PA317 supernatant

containing retroviral vectors with either the 537, 558 or 560 genomes

* genomes packaged in PA317 cells

5

Although the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of

10

the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT:
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as represented by
The Secretary of the Department
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 - (H) TELEFAX: (301) 402-0220
 - (I) TELEX:
- (ii) TITLE OF INVENTION: Gibbon Ape Leukemia Virus-Based
Retroviral Vectors
- (iii) NUMBER OF SEQUENCES: 5
- (iv) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (v) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: WO not yet assigned
 - (B) FILING DATE: 06-APR-1994
 - (C) CLASSIFICATION:
- (vii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Bastian,, Kevin L.
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- (ix) TELECOMMUNICATION INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8535 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..8535
- (D) OTHER INFORMATION: /standard_name= "GaLV SEATO Genome"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AATGAAAGAA GTGTTTTTTT TTAGCCAACG GCAGTAACGC CATTTTGCTA GGCACACCTA	60
AAGGATAGGA AAAATACAGC TAAGAACAGG GCCAAACAGG ATATCTGTGG TCATGCACCT	120
GGGCCCCGGC CCAGGCCAAG GACAGAGGGT TCCCAGAAAT AGATGAGTCA ACAGCAGTTT	180
CCAGCAAGGA CAGAGGGTTC CCAGAAATAG ATGAGTCAAC AGCAGTTTCC AGGGTGCCCC	240
TCAACCGTTT CAAGGACTCC CATGACCGGG AATTCACCCC TGGCCTTATT TGAACCTAAC	300
AATTACCTTG CCTCTCGCTT CTGTACCCGC GCTTTTTGCT ATAAAAATAA GCTCAGAAAC	360
TCCACCCGGA GCGCCAGTCC TTAGAGAGAC TGAGCCGCCC GGTACCCGT GTGTCCAATA	420
AAACCTCTTG CTGATTGCAT CCGGAGCCGT GGTCTCGTTG TTCCTGGGA GGGTTTCTCC	480
TAACCTATTGA CCGCCCACTT CGGGGGTCTC ACATTGTTGGG GCTCGTCCGG GATCGGAAAC	540
CCCACCCAGG GACCACCGAC CCACCAACGG GAGGTAAGCT GGCCAGCGAC CGTTGTGTGT	600
CTCGCTTCTG TGTCTAAGTC CGTAATTCTG ACTGTCCTTG TGTGTCTCGC TTTGTGTCT	660
GAGACCGTAA CTCTGACTGC CTTGTAAAGT GCGCGCATTT TTTTGGTTTC AGTCTGTTCC	720
GGGTGAATCA CTCGCGGAGT GACGTGTGAG TAGCGAACAG ACGTGTTCCG GGCTCACCGC	780
CTGGTAATCC AGGGAGACGT CCCAGGATCA GGGGAGGACC AGGGACGCCT GGTGGACCCC	840
TCGGTAACGG GTCGTTGTGA CCCGATTTC TCGCCCGTCT GGTAAAGACGC GCTCTGAATC	900
TGATTCTCTC TCTCGGTCTG CTCGCGCCCG TCTCTGGTTT CTTTTGTTT CGTTTCTGGA	960
AAGCCTCTGT GTCACAGTCT TTCTCTCCCA AATCATCAAT ATGGGACAAG ATAATTCTAC	1020
CCCTATCTCC CTCACTCTAA ATCACTGGAG AGATGTGAGA ACAAGGGCTC ACAATCTATC	1080
CGTGGAATC AAAAAGGGAA AATGGCAGAC TTTCTGTTCC TCCGAGTGGC CCACATTCGG	1140
CGTGGGGTGG CCACCGGAGG GAACTTTTAA TCTCTCTGTC ATTTTGCAG TTAATAAGAT	1200
TGTCTTTCAG GAGAACGGGG GACATCCGGA CCAAGTTCCA TATATCGTGG TATGGCAGGA	1260
CCTCGCCCAG AATCCCCCAC CATGGGTGCC AGCCTCCGCC AAGGTCGCTG TTGTCTCTGA	1320
TACCCGAAGA CCAGTTGCGG GGAGGCCATC AGCTCCTCCC CGACCCCCCA TCTACCCGGC	1380
AACAGACGAC TTAATCCTCC TCTCTGAACC CACGCCCCCG CCCTATCCGG CGGCACTGCC	1440
ACCCCTCTG GCCCCTCAGG CGATCGGACC GCCGTCAGGC CAGATGCCCG ATAGTAGCGA	1500

TCCTGAGGGG	CCAGCCGCTG	GGACCAGGAG	TCGCCGTGCC	CGCAGTCCAG	CAGACAACCTC	1560
GGGTCCTGAC	TCCACTGTGA	TTTTGCCCCCT	CCGAGCCATA	GGACCCCCCG	CCGAGCCCAA	1620
TGGCCTGGTC	CCTCTACAAT	ATTGGCCCTT	TTCCTCAGCA	GATCTTTATA	ATTGGAAATC	1680
TAATCATCCC	TCTTTTTCTG	AAAACCCAGC	AGGTCTCACG	GGGCTCCTTG	AGTCTCTTAT	1740
GTTCTCCCAT	CAGCCCACCT	GGGACGATTG	CCAACAGCTC	CTACAGATTC	TTTTCAACCAC	1800
TGAGGAACGG	GAAAGAATTC	TCCTGGAGGC	CCGCAAAAAT	GTCCTTGGGG	ACAATGGGGC	1860
CCCTACACAG	CTCAGAACC	TCATTAATGA	GGCCTTCCCC	CTCAATCGAC	CTCACTGGGA	1920
TTACAACACA	GCCGCAGGTA	GGGAGCGTCT	TCTGGTCTAC	CGCCGGACTC	TAGTGGCAGG	1980
TCTCAAAGGG	GCAGCTCGGC	GTCCTACCAA	TTTGGCTAAG	GTAAGAGAGG	TCTTGCAGGG	2040
ACCGGCAGAA	CCCCCTTCGG	TTTTCTTAGA	ACGCCTGATG	GAGGCCTATA	GGAGATACAC	2100
TCCGTTTGAT	CCCTCTTCTG	AGGGACAACA	GGCTGCGGTC	GCCATGGCCT	TTATCGGACA	2160
GTCAGCCCCA	GATATCAAGA	AAAAGTTACA	GAGGCTAGAG	GGGCTCCAGG	ACTATTCCTT	2220
ACAAGATTTA	GTAAAAGAGG	CAGAAAAGGT	GTACCATAAG	AGAGAGACAG	AAGAAGAAAG	2280
ACAAGAAAGA	GAAAAAAGG	AGGCAGAAGA	AAAGGAGAGG	CGGCGCGATA	GGCCGAAGAA	2340
AAAAAACTTG	ACTAAAATTC	TGGCCGCAGT	AGTAAGTAGA	GAAGGGTCCA	CAGGTAGGCA	2400
GACAGGGAAC	CTGAGCAACC	AGGCAAAGAA	GACACCTAGG	GATGGAAGAC	CTCCACTAGA	2460
CAAAGACCAG	TGCGCATACT	GTAAAGAGAA	GGGCCATTGG	GCAAGAGAAT	GTCCCCGAAA	2520
AAAACACGTC	AGAGAAGCCA	AGGTTCTAGC	CCTAGATAAC	TAGGGGAGTC	AGGGTTCCGA	2580
CCCCCTCCCC	GAACCTAGGG	TAACACTGAC	TGTGGAGGGG	ACCCCCATTG	AGTTCTCTGGT	2640
CGACACCGGA	GCTGAACATT	CAGTATTGAC	CCAACCCATG	GGAAAAGTAG	GGTCCAGACG	2700
GACGGTCGTG	GAAGGAGCGA	CAGGCAGCAA	GGTCTACCCC	TGGACCACAA	AAAGACTTTT	2760
AAAAATTGGA	CATAACAAG	TGACCCACTC	CTTCTGGTGC	ATACCCGAGT	GCCCTGCTCC	2820
TCTGTTGGGC	AGGGACCTCC	TAACCAAAC	AAAGGCCCCAG	ATCCAGTTTT	CCGCTGAGGG	2880
CCCACAGGTA	ACATGGGGAG	AACGCCCTAC	TATGTGCCTG	GTCCTAAACC	TGGAAGAAGA	2940
ATACCGACTA	CATGAAAAGC	CAGTACCCTC	CTCTATCGAC	CCATCCTGGC	TCCAGCTTTT	3000
CCCCACTGTA	TGGGCAGAAA	GAGCCGGCAT	GGGACTAGCC	AATCAAGTCC	CACCACTGGT	3060
AGTAGAGCTA	AGATCAGGTG	CCTCACCAGT	GGCTGTTCGA	CAATATCCAA	TGAGCAAAGA	3120
AGCTCGGGAA	GGTATCAGAC	CCCACATCCA	GAAGTTCCTA	GACCTAGGGG	TCTTGGTGCC	3180
CTGTCGGTCG	CCCTGGAATA	CCCCTCTGCT	ACCTGTAAAA	AAGCCAGGGA	CCAATGACTA	3240
TCGGCCAGTT	CAAGACCTGA	GAGAAATTAA	TAAAAGGGTA	CAGGATATTC	ATCCCACAGT	3300
CCCAAACCCCT	TACAATCTTC	TGAGTTCCCT	TCCGCCTAGC	TATACTTGGT	ACTCAGTCTT	3360
AGATCTCAAG	GATGCCTTTT	TCTGCCTCAG	GCTACATCCC	AACAGCCAGC	CGCTGTTCCG	3420
GTTTCGAGTGG	AAAGACCCAG	AAAAAGGTAA	CACAGGTCAG	CTGACCTGGA	CGCGGCTACC	3480
ACAAGGGTTC	AAGAACTCTC	CCACTCTCTT	CGACGAGGCC	CTCCACCGAG	ATTTGGCTCC	3540
CTTTAGGGCC	CTCAACCCCC	AGGTGGTGTT	ACTCCAATAT	GTGGACGACC	TCTTGGTGGC	3600

CGCCCCCACA	TATGAAGACT	GCAAAAAAGG	AACACAGAAG	CTCTTACAGG	AGTTAAGTAA	3660
GTTGGGGTAC	CGGGTATCGG	CTAAGAAGGC	CCAGCTCTGC	CAGAGAGAAG	TCACCTATCT	3720
GGGGTACCTA	CTCAAGGAAG	GAAAAAGATG	GCTAACCCCA	GCCCGAAAGG	CTACTGTTAT	3780
GAAAATCCCT	GTTCCCTACG	CCCCCAGACA	GGTCCGTGAA	TTTCTAGGCA	CTGCCGGATT	3840
CTGCAGGCTC	TGGATCCCTG	GGTTTGCTTC	CCTGGCTGCA	CCCTTGTACC	CCCTAACAAA	3900
AGAGAGCATC	CCTTTTATTT	GGACTGAGGA	ACATCAGCAG	GCTTTTGACC	ACATAAAAAA	3960
AGCCTTGCTG	TCAGCCCCTG	CATTGGCCCT	CCCAGACCTC	ACCAAGCCAT	TCACTCTATA	4020
TATAGATGAG	AGAGCCGGCG	TGGCCCCGGG	AGTGCTCACT	CAGACTTTAG	GACCCTGGCG	4080
GCGGCCAGTA	GCATATCTAT	CAAAAAAAT	GGATCCGGTG	GCCAGCGGGT	GGCCAACCTG	4140
CCTGAAAGCG	GTTGCAGCAG	TAGCACTCCT	TCTCAAAGAC	GCTGATAAGT	TAACCTTGGG	4200
ACAAAATGTG	ACTGTGATTG	CTTCCCATAG	CCTCGAAAGC	ATCGTGCGGC	AACCCCCCGA	4260
CCGGTGGATG	ACCAATGCCA	GAATGACTCA	TTACCAGAGC	CTGCTGTAA	ATGAAAGGGT	4320
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CACCCAGTG	CACAGGTGCT	CAGAAATCCT	CGCCGAAGAA	ACTGGAATC	GACGAGACCT	4440
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GGAAGGTAAA	CGGAGAGCAG	GGGCCCCGAT	CGTAGATGGC	AAGCGGACGG	TATGGGCTAG	4560
CAGCCTGCCA	GAAGGTACGT	CAGCCCAGAA	GGCTGAACTA	GTAGCCTTGA	CGCAGGCATT	4620
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TGCTCATATT	CATGGGGCAA	TATATAAGCA	GAGGGGGCTG	CTCACTTCTG	CTGGAAAAGA	4740
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AAAACCTCAA	GAGCCAATCG	AGCCCGCTCA	AGAAAAGACC	AGGCCGAGGG	AGCTCACCCC	4980
TGACCGGGGA	AAAGAATTCA	TTAAGCGGTT	ACATCAGTTA	ACTCACTTAG	GACCAGAAAA	5040
GCTTCTCCAA	CTAGTGAACC	GTACCAGCCT	CCTCATCCCG	AACCTCCAAT	CTGCAGTTCG	5100
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GACCTTGACC	AAATTAGCCT	TAGAGACCGG	TGGAAAAGAC	TGGGTGACCC	TCCTTCCCTT	5580
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CCCAAGGAAA	GCTCACCCTC	ACTGAGGTCT	CAGGACACGG	GTTGTGCATA	GGAAAGGTGC	7140
CCTTTACCCA	TCAGCATCTC	TGCAATCAGA	CCCTATCCAT	CAATTCCTCC	GGAGACCATC	7200
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TAGACCACTC	AGGTGCAGTA	CGGGACTCCA	TGAAAAAACT	CAAAGAAAAA	CTGGATAAAA	7740
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TTTGCTCTAA	GATTAGAGCT	ATTCACAAGA	GAAATGGGGG	AATGAAAGAA	GTGTTTTTTT	8040
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CATGACCGGG	AATTCACCCC	TGGCCTTATT	TGAACTAACC	AATTACCTTG	CCTCTCGCTT	8340
CTGTACCCGC	GCTTTTTGCT	ATAAAATAAG	CTCAGAAACT	CCACCCGGAG	CGCCAGTCCT	8400
TAGAGAGACT	GAGCCGCCCC	GGTACCCGTG	TGTCCAATAA	AACCTCTTGC	TGATTGCATC	8460
CGGAGCCGTG	GTCTCGTTGT	TCCTTGGGAG	GGTTTCTCCT	AACTATTGAC	CGCCCACTTC	8520
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 564 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: LTR
- (B) LOCATION: 1..564
- (D) OTHER INFORMATION: /standard_name= "3' LTR of GaLV SEATO"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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GGGCCCCGGC CCAGGCCAAG GACAGAGGGT	TCCCAGAAAT	AGATGAGTCA	ACAGCAGTTT	180
CCAGCAAGGA CAGAGGGTTC CCAGAAATAG	ATGAGTCAAC	AGCAGTTTCC	AGCAAGGACA	240
GAGGGTTCCC AGAAATAGAT GAGTCAACAG	CAGTTTCCAG	AGGGTGCCCC	TCAACCGTTT	300
CAAGGACTCC CATGACCGGG AATTCACCCC	TGGCCTTATT	TGAACTAACC	AATTACCTTG	360
CCTCTCGCTT CTGTACCCGC GCTTTTTGCT	ATAAAAATAA	GCTCAGAAAC	TCCACCCGGG	420
CGCCAGTCCT TAGAGAGACT GAGCCGCCCC	GGTACCCGTG	TGTCCAATAA	AACCTCTTGC	480
TGATTGCATC CGGAGCCGTG GTCTCGTTGT	TCCTTGGGAG	GGTTTCTCCT	AACTATTGAC	540
CGCCCACTTC GGGGGTCTCA CATT				564

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9661 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..9613
- (D) OTHER INFORMATION: /standard_name= "p558 retroviral vector"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATTTAGGTGA CACTATAGAA CTCGAGGAAT TCTGAAAGAA GTGTTTTTCA AGTTAGCTGC	60
AGTAACGCCA TTTTGCTAGG CACACCTAAA GGATAGGAAA AATACAGCTA AGAACAGGGC	120
CAAACAGGAT ATCTGTGGTC ATGCACCTGG GCCCCGGCCC AGGCCAAGGA CAGAGGGTTC	180
CCAGAAATAG ATGAGTCAAC AGCAGTTTCC AGCAAGGACA GAGGGTTCCC AGAAATAGAT	240
GAGTCAACAG CAGTTTCCAG GGTGCCCCCTC AACCCTTTCA AGGACTCCCA TCACCGGGAA	300
TTCACCCCTG GCCTTATTTG AACTAACCAA TTACCTTGCC TCTCGCTTCT GTACCCGGCG	360
TTTTTGCTAT AAAAATAAGC TCAGAACTC CACCCGGAGC GCCAGTCCTT AGAGAGACTG	420
AGCCGCCCCG GTACCCGTGT GTCCAATAAA ACCTCTTGCT GATTGCATCC GGAGCCGTGG	480
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ATTTGGGGGC TCGTCCGGA TCGGAAACCC CACCCAGGGA CCACCGACCC ACCAACGGGA	600
GGTAAGCTGG CCAGCGACCG TTGTGTGTCT CGCTTCTGTG TCTAAGTCCG TAATTCTGAC	660
TGTCCTTGTT TGTCTCGCTT CTGTGTCTGA GACCGTAACT CTGACTGCCC TTGTAAGTGC	720
GCGCATTTTT TTGGTTTCAG TCTGTTCCGG GTGAATCACT CTGCGAGTGA CGTGTGAGTA	780
GCGAACAGAC GTGTTTCGGGG CTCACCGCCT GGTAATCCAG GGAGACGTCC CAGGATCAGG	840
GGAGGACCAG GGACGCCTGG TGGACCCCTC GGTAACGGGT CGTTGTGACC CGATTTCATC	900
GCCCCGTCTG TAAGACGCGC TCTGAATCTG ATTCTCTCTC TCGGTGCGCT CGCCGCCGTC	960
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TCATCAATAT GGGACAAGAT AATTCTACCC CTATCTCCCT CACTCTAAAT CACTGGAGAG	1080
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CCTCCGCCAA GGTGCTGTT GTCTCTGATA CCCGAAGACC AGTTGCGGGG AGGCCATCAG	1380
CTCCTCCCCG ACCCCCCATC TACCCGGCAA CAGACGACTT ACTCCTCTC TCTGAACCCA	1440
CGCCCCCGCC CTATCCGGCG GCACTGCCAC CCCCTCTGGC CCCTCAGGCG ATCGGACCGC	1500

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CCTCAGCAGA	TCCCGTCGTT	TTACAACGTC	GTGACTGGGA	AAACCCTGGC	GTTACCCAAC	1740
TTAATCGCCT	TGCAGCACAT	CCCCCTTTTCG	CCAGCTGGCG	TAATAGCGAA	GAGGCCCCGCA	1800
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CCTATCCCAT	TACGGTCAAT	CCGCCGTTTG	TTCCCACGGA	GAATCCGACG	GGTTGTTACT	2040
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CGTATTGGGC	GCTCTTCCGC	TTCTCGCTC	ACTGACTCGC	TGCGCTCGGT	CGTTCGGCTG	7440
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AACGCAGGAA	AGAACATGTG	AGCAAAAGGC	CAGCAAAAGG	CCAGGAACCG	TAAAAAGGCC	7560
GCGTTGCTGG	CGTTTTTCCA	TAGGCTCCGC	CCCCCTGACG	AGCATCACAA	AAATCGACGC	7620
TCAAGTCAGA	GGTGGCGAAA	CCCGACAGGA	CTATAAAGAT	ACCAGGCGTT	TCCCCCTGGA	7680
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GCTGGTAGCG	GTGGTTTTTT	TGTTTGCAAG	CAGCAGATTA	CGCGCAGAAA	AAAAGGATCT	8160
CAAGAAGATC	CTTTGATCTT	TTCTACGGGG	TCTGACGCTC	AGTGGAACGA	AAACTCACGT	8220
TAAGGGATTT	TGGTCATGAG	ATTATCAAAA	AGGATCTTCA	CCTAGATCCT	TTTAAATTAA	8280
AAATGAAGTT	TTAAATCAAT	CTAAAGTATA	TATGAGTAAA	CTTGGTCTGA	CAGTTACCAA	8340
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TGACTCCCCG	TCGTGTAGAT	AACTACGATA	CGGGAGGGCT	TACCATCTGG	CCCCAGTGCT	8460
GCAATGATAC	CGCGAGACCC	ACGCTCACCG	GCTCCAGATT	TATCAGCAAT	AAACCAGCCA	8520
GCCGGAAGGG	CCGAGCGCAG	AAGTGGTCCT	GCAACTTTAT	CCGCCTCCAT	CCAGTCTATT	8580
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GGTTCCCAAC	GATCAAGGCG	AGTTACATGA	TCCCCCATGT	TGTGCAAAAA	AGCGGTTAGC	8760
TCCTTCGGTC	CTCCGATCGT	TGTCAGAAGT	AAGTTGGCCG	CAGTGTTATC	ACTCATGGTT	8820
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GGTGAGTACT	CAACCAAGTC	ATTCTGAGAA	TAGTGTATGC	GGCGACCGAG	TTGCTCTTGC	8940
CCGGCGTCAA	TACGGGATAA	TACCGCGCCA	CATAGCAGAA	CTTTAAAAGT	GCTCATCATT	9000
GGAAAACGTT	CTTCGGGGCG	AAAACCTCTCA	AGGATCTTAC	CGCTGTTGAG	ATCCAGTTCC	9060
ATGTAACCCA	CTCGTGCACC	CAACTGATCT	TCAGCATCTT	TTACTTTTAC	CAGCGTTTCT	9120
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TATAAAAATA	GGCGTATCAC	GAGGCCCTTT	CGTCTCGCGC	GTTTCGGTGA	TGACGGTGAA	9420
AACCTCTGAC	ACATGCAGCT	CCCGGAGACG	GTCACAGCTT	GTCTGTAAGC	GGATGCCGGG	9480
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A 9661

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10306 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..10258
- (D) OTHER INFORMATION: /standard_name= "p521 retroviral vector"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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GGAAAGTTCA GATCAAGGTC AGGAACAAAG AACAGCTGA ATACCAAACA GGATATCTGT 180
GGTAAGCGGT TCCTGCCCCC GGCTCAGGGC CAAGAACAGA TGAGACAGCT GAGTGATGGG 240
CCAAACAGGA TATCTGTGGT AAGCAGTTCC TGCCCCGGCT CGGGGCCAAG AACAGATGGT 300
CCCCAGATGC GGTCCAGCCC TCAGCAGTTT CTAGTGAATC ATCAGATGTT TCCAGGGTGC 360
CCCAAGGACC TGAAAATGAC CCTGTACCTT ATTTGAATA ACCAATCAGT TCGCTTCTCG 420
CTTCTGTTCG CGCGCTTCCG CTCTCCGAGC TCAATAAAAG AGCCCACAAC CCCTCACTCG 480
GCGCGCCAGT CTTCCGATAG ACTGCGTCGC CCGGGTACCC GTATTCCCAA TAAAGCCTCT 540
TGCTGTTTGC ATCCGAATCG TGGTCTCGCT GTTCCTTGGG AGGGTCTCCT CTGAGTGATT 600
GACTACCCAC GACGGGGGTC TTTCATTGCG GGGCTCGTCC GGGATTGGA GACCCCTGCC 660
CAGGGACCAC CGACCCACCA CCGGGAGGTA AGCTGGCCAG CAACCTATCT GTGTCTGTCC 720
GATTGTCTAG TGTCTATGTT TGATGTTATG CGCCTGCGTC TGTACTAGTT AGCTAACTAG 780
CTCTGTATCT GCGCGACCCG TGGTGGAAC TACGAGTTCT GAACACCCCG CCGCAACCCA 840
GGGAGACGTC CCAGGGACTT TGGGGGCCGT TTTTGTGGCC CGACCTGAGG AAGGGAGTCG 900
ATGTGGAATC CGACCCCGTC AGGATATGTG GTTCTGGTAG GAGACGAGAA CCTAAAACAG 960
TTCCCGCCTC CGTCTGAATT TTTGCTTTCG GTTTGGAACC GAAGCCGCGC GTCTTGCTCTG 1020
CTGCAGCATC GTTCTGTGTT GTCTCTGTCT GACTGTGTTT CTGTATTTGT CTGAAAATTA 1080
GGGCCAGACT GTTACCACTC CCTTAAGTTT GACCTTAGGT CACTGGAAAG ATGTCGAGCG 1140
GATCGCTCAC AACCAGTCGG TAGATGTCAA GAAGAGACGT TGGGTTACCT TCTGCTCTGC 1200
AGAATGGCCA ACCTTTACGT CGGATGGCCG CGAGACGGCA CCTTTAACCG AGACCTCATC 1260
ACCCAGGTTA AGATCAAGGT CTTTTCACCT GGCCCGCATG GACACCCAGA CCAGGTCCCC 1320

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CACCCTAAGC	CTCCGCCTCC	TCTTCCTCCA	TCCGCCCCGT	CTCTCCCCCT	TGAACCTCCT	1440	
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TTACGGATTC	GGATCCCGTC	GTTTTACAAC	GTCGTGACTG	GGAAAACCCT	GGCGTTACCC	1620	
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GCACCGATCG	CCCTTCCCAA	CAGTTGCGCA	GCCTGAATGG	CGAATGGCGC	TTTGCCTGGT	1740	
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ACTCGCTCAC	ATTTAATGTT	GATGAAAGCT	GGCTACAGGA	AGGCCAGACG	CGAATTATTT	1980	
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GCCTCGCGGT	GATGGTGCTG	CGTTGGAGTG	ACGGCAGTTA	TCTGGAAGAT	CAGGATATGT	2160	
GGCGGATGAG	CGGCATTTTC	CGTGACGTCT	CGTTGCTGCA	TAAACCGACT	ACACAAATCA	2220	
GCGATTTCCA	TGTTGCCACT	CGCTTTAATG	ATGATTTTCA	CCGCGCTGTA	CTGGAGGCTG	2280	
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TGCTGAACGG	CAAGCCGTTG	CTGATTGAG	GCGTTAACCG	TCACGAGCAT	CATCCTCTGC	2640	
ATGGTCAGGT	CATGGATGAG	CAGACGATGG	TGCAGGATAT	CCTGCTGATG	AAGCAGAACA	2700	
ACTTTAACGC	CGTGCGCTGT	TCGATTATC	CGAACCATCC	GCTGTGGTAC	ACGCTGTGCG	2760	
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GCCACGGCGC	TAATCACGAC	GCGCTGTATC	GCTGGATCAA	ATCTGTGAT	CCTTCCCGCC	3000	
CGGTGCAGTA	TGAAGGCGGC	GGAGCCGACA	CCACGGCCAC	CGATATTATT	TGCCCCGATG	3060	
ACGCGCGCGT	GGATGAAGAC	CAGCCCTTCC	CGGCTGTGCC	GAAATGGTCC	ATCAAAAAAT	3120	
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ACCCGTGGTC	GGCTTACGGC	GGTGATTTTG	GCGATACGCC	GAACGATCGC	CAGTTCTGTA	3360	
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CGGAAAACCT	CAGTGTGACG	CTCCCCGCGG	CGTCCCACGC	CATCCCGCAT	CTGACCACCA	3780
GCGAAATGGA	TTTTTGATC	GAGCTGGGTA	ATAAGCGTTG	GCAATTTAAC	CGCCAGTCAG	3840
GCTTTCTTTC	ACAGATGTGG	ATTGGCGATA	AAAAACAAC	GCTGACGCCG	CTGCGCGATC	3900
AGTTCACCCG	TGCACCGCTG	GATAACGACA	TTGGCGTAAG	TGAAGCGACC	CGCATTGACC	3960
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TCCCCTTGGT	TCACTACCCT	GCTATCAACC	ATCGCTGGGC	CCCTATTACT	CCTCCTTCTG	6420
TTGCTCATCC	TCGGGCCATG	CATCATCAAT	AAGTTAGTTC	AATTCATCAA	TGATAGGATA	6480
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GGCCAAGGAC	AGAGGGTTCC	CAGAAATAGA	TGAGTCAACA	GCAGTTTCCA	GCAAGGACAG	6780
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GAGACGAAAG	GGCCTCGTGA	TACGCCTATT	TTTATAGGTT	AATGTCATGA	TAATAATGGT	8100
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CTCATATATA	CTTTAGATTG	ATTTAAAACT	TCATTTTAA	TTTAAAAGGA	TCTAGGTGAA	9180
GATCCTTTTT	GATAATCTCA	TGACCAAAAT	CCCTTAACGT	GAGTTTTTCG	TCCACTGAGC	9240
GTCAGACCCC	GTAGAAAAGA	TCAAAGGATC	TTCTTGAGAT	CCTTTTTTTC	TGCGCGTAAT	9300
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CCTCGCTCTG	CTAATCCTGT	TACCAGTGGC	TGCTGCCAGT	GGCGATAAGT	CGTGTCTTAC	9540
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TATTACCGCC	TTTGAGTGAG	CTGATACCGC	TCGCCGCAGC	CGAACGACCG	AGCGCAGCGA	10020
GTCAGTGAGC	GAGGAAGCGG	AAGAGCGCCC	AATACGCAAA	CCGCCTCTCC	CCGCGCGTTG	10080
GCCGATTCAT	TAATGCAGCT	GGCACGACAG	GTTTCCCGAC	TGGAAAGCGG	GCAGTGAGCG	10140
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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10970 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..10970
- (D) OTHER INFORMATION: /standard_name= "p537 retroviral vector"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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WHAT IS CLAIMED IS:

1. A recombinant DNA construct comprising a defective viral genome comprising a polynucleotide sequence of interest and a gibbon ape leukemia virus (GaLV) component.

2. The construct of claim 1, wherein the GaLV component includes a GaLV packaging site.

3. The construct of claim 2, wherein the packaging site consists of between about 150 base pairs and about 1500 base pairs.

4. The construct of claim 2, wherein the packaging site consists essentially of a sequence extending from about position 200 to about position 910 of the sequence shown in Figure 1.

5. The construct of claim 1, wherein the GaLV component includes regulatory sequences which direct expression of the polynucleotide of interest.

6. The construct of claim 5, wherein the regulatory sequences are from a GaLV 3' LTR.

7. The construct of claim 6, wherein the promoter is from GaLV SF.

8. A mammalian cell comprising the defective viral genome of claim 1.

9. The cell of claim 8, further comprising retroviral gag and pol genes.

10. The cell of claim 9, wherein the gag and pol genes are from GaLV SF or GaLV SEATO.

11. The cell of claim 9, wherein the *gag* and *pol* genes are from MoMLV.

12. The cell of claim 8, further comprising a retroviral *env* gene.

13. The cell of claim 12, wherein the *env* gene is from GaLV SF or GaLV SEATO.

14. The cell of claim 8, which is PG13 or PA317.

15. An isolated hybrid virion comprising GaLV envelope proteins and an RNA genome comprising a polynucleotide sequence of interest and a GaLV component.

16. The virion of claim 15, further comprising GaLV core proteins.

17. The virion of claim 15, further comprising MoMLV core proteins.

18. The virion of claim 15, wherein the envelope proteins are GaLV SF proteins.

19. The virion of claim 15, wherein the GaLV sequence includes a packaging site.

20. The virion of claim 19, wherein the packaging site is transcribed from a sequence consisting of between about 150 base pairs and about 1500 base pairs.

21. The virion of claim 19, wherein the packaging site is transcribed from a polynucleotide sequence extending from about position 200 to about position 910 of the sequence shown in Figure 1.

22. An isolated recombinant DNA construct comprising a polynucleotide sequence which encodes an

infectious GaLV virion capable of infecting a mammalian cell and producing infectious viral progeny.

23. The construct of claim 22, wherein the
5 DNA construct comprises GaLV SF sequences and GaLV SEATO sequences.

24. The construct of claim 23, wherein the DNA
10 construct comprises 97% GaLV SEATO sequences and 3% GaLV SF sequences.

25. A method of introducing a polynucleotide of interest into human cells having a GaLV receptor, the method comprising:

15 contacting the cells with hybrid virions comprising GaLV envelope proteins and an RNA genome comprising the polynucleotide sequence of interest and a GaLV packaging site; and

20 selecting cells having the polynucleotide of interest.

26. The method of claim 25, further comprising implanting the cells in a human patient.

25 27. The method of claim 25, wherein the human cells are selected from the group consisting of bone marrow cells and tumor infiltrating cells.

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[illegible]

Figure 1

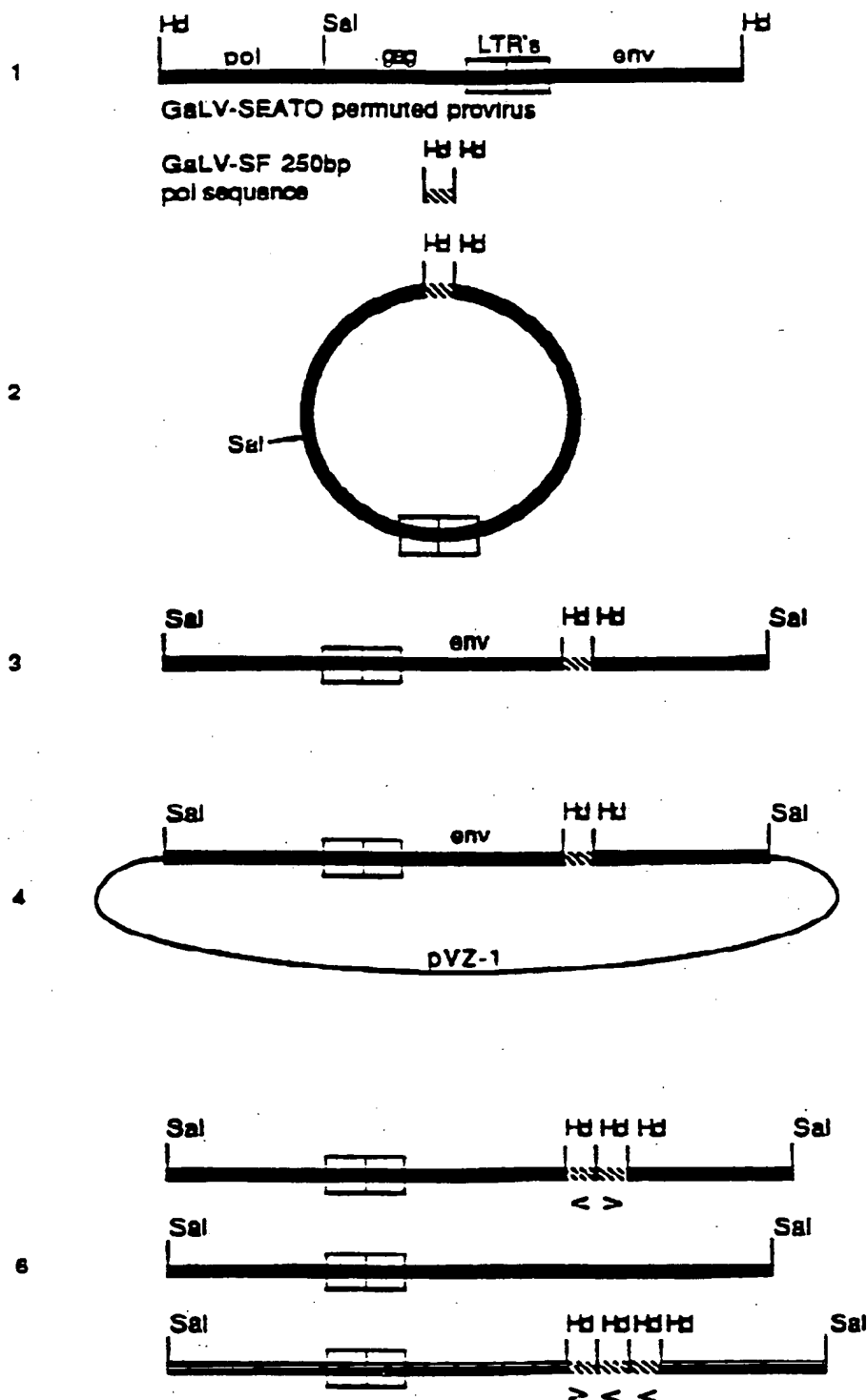
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FIG. 1—Continued

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FIGURE 2A
STEP

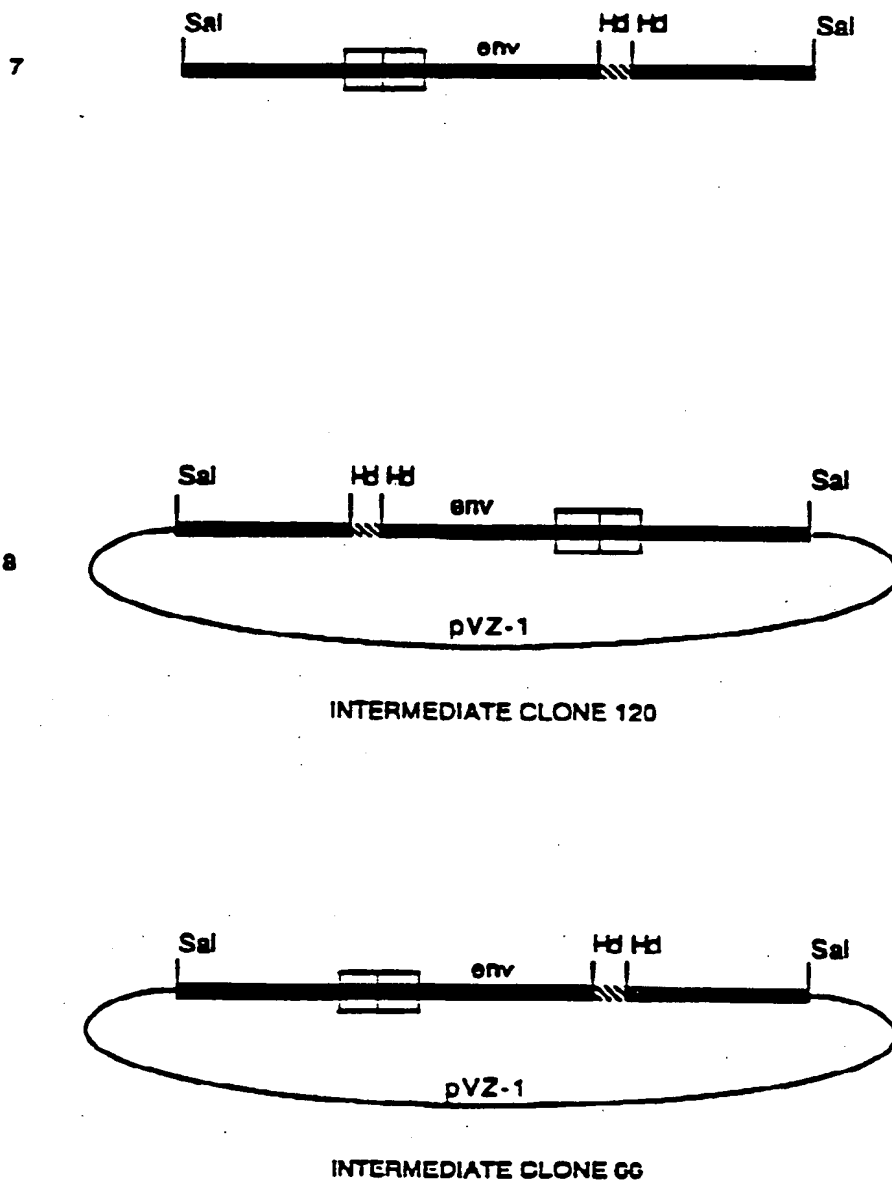
REPAIR OF POL GENE OF GALV SEATO



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FIGURE 2B
STEP

CHANGE OF GALV SEATO INSERT ORIENTATION

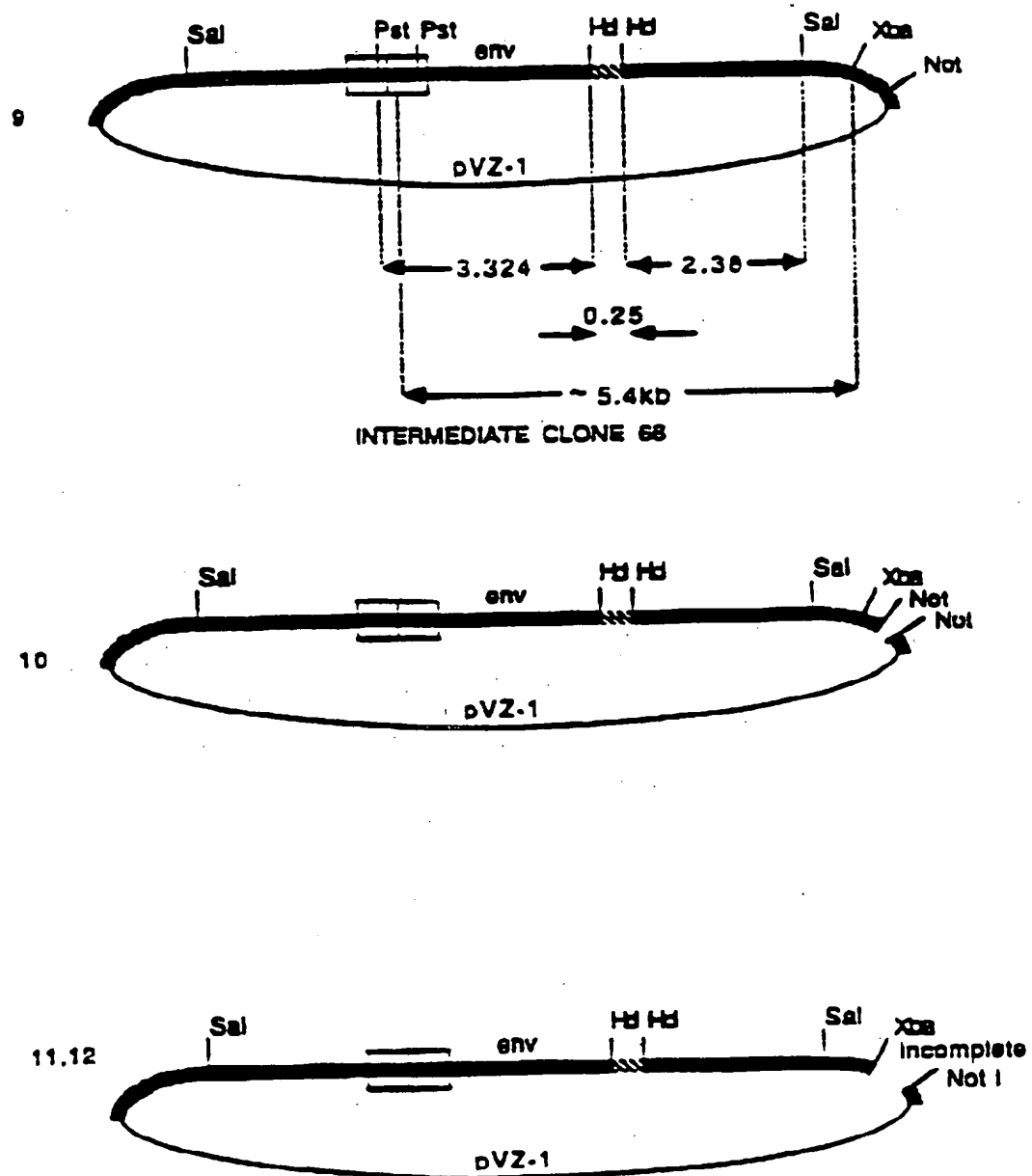


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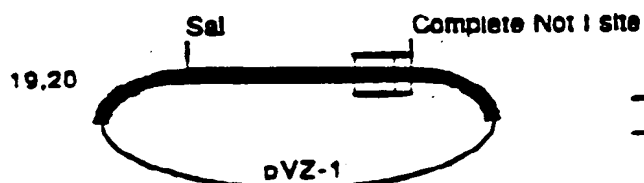
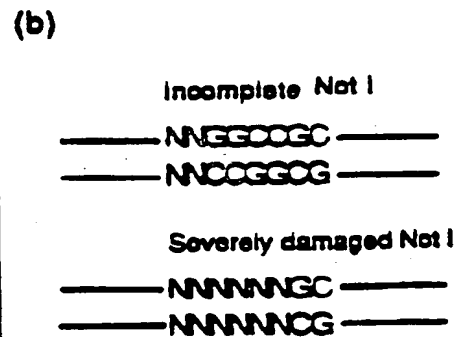
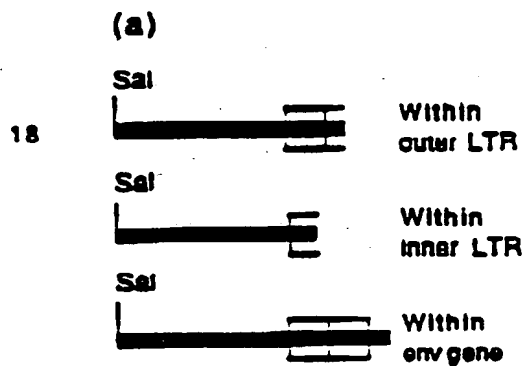
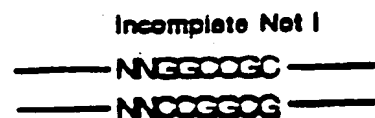
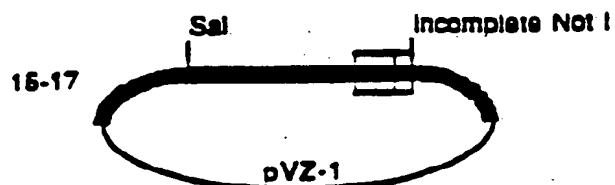
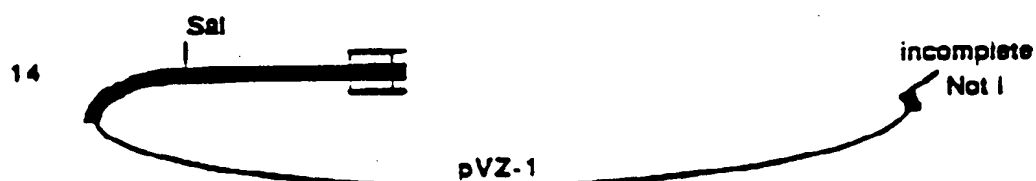
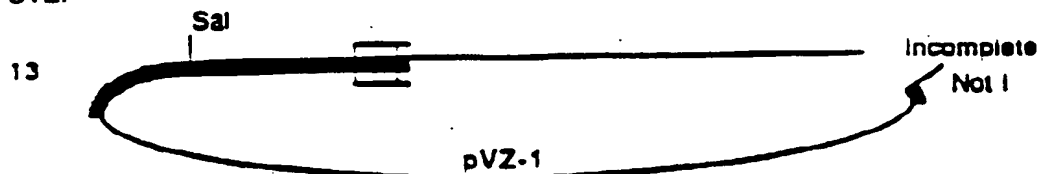
FIGURE 2C INTERMEDIATE CLONE 68: UNIDIRECTIONAL DECREASE
IN INSERT LENGTH USING EXONUCLEASES III AND VII

STEP



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FIGURE 2D STEP



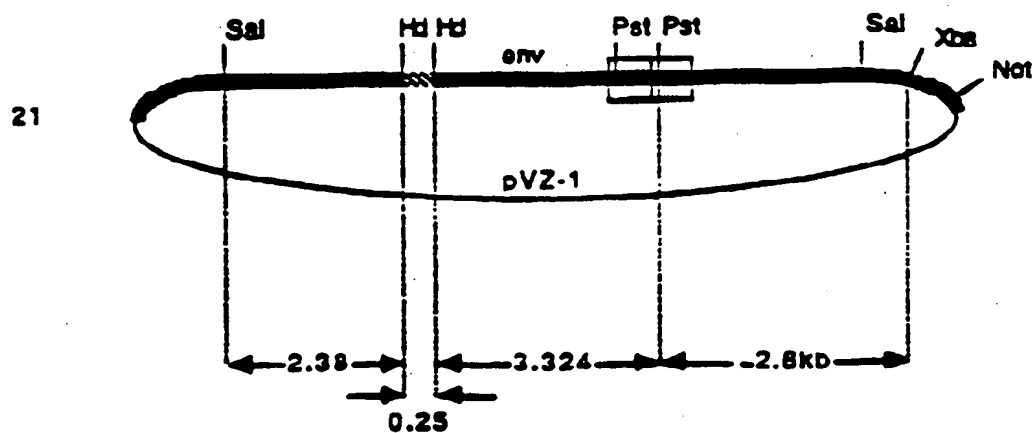
INTERMEDIATE CLONE G6Exo52

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FIGURE 2E

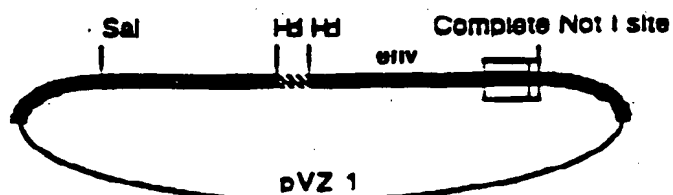
INTERMEDIATE CLONE 120: UNIDIRECTIONAL DECREASE
IN INSERT LENGTH USING EXONUCLEASES III AND VII

STEP



INTERMEDIATE CLONE 120

22-32



Complete Not I site



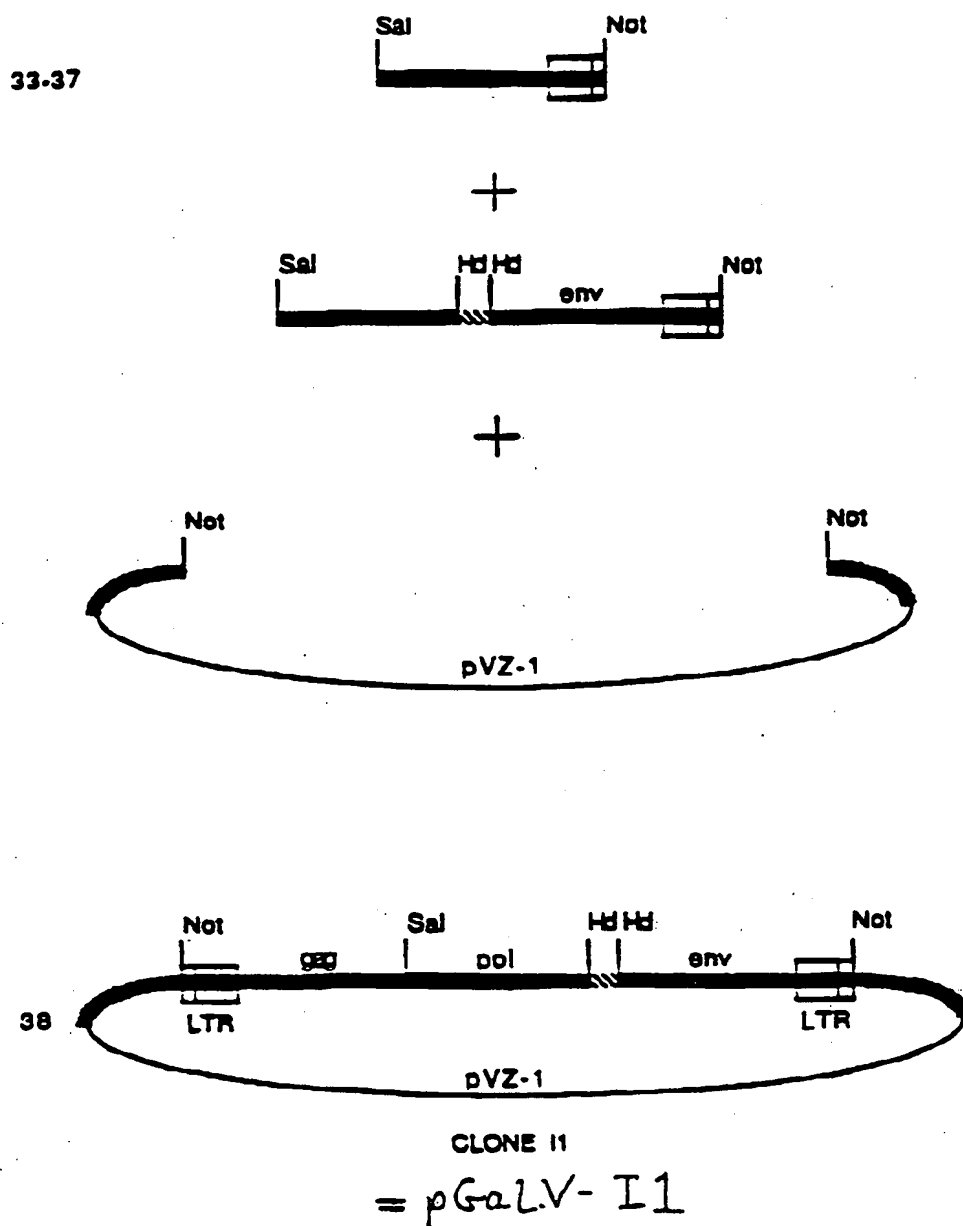
INTERMEDIATE CLONE 120Exo55

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FIGURE 2F

COUPLING OF CLONE 66Ex052 INSERT AND
CLONE 120Ex055 INSERT: SEPARATION OF LTR'S AND
GENERATION OF POTENTIAL INFECTIOUS CLONE

STEP



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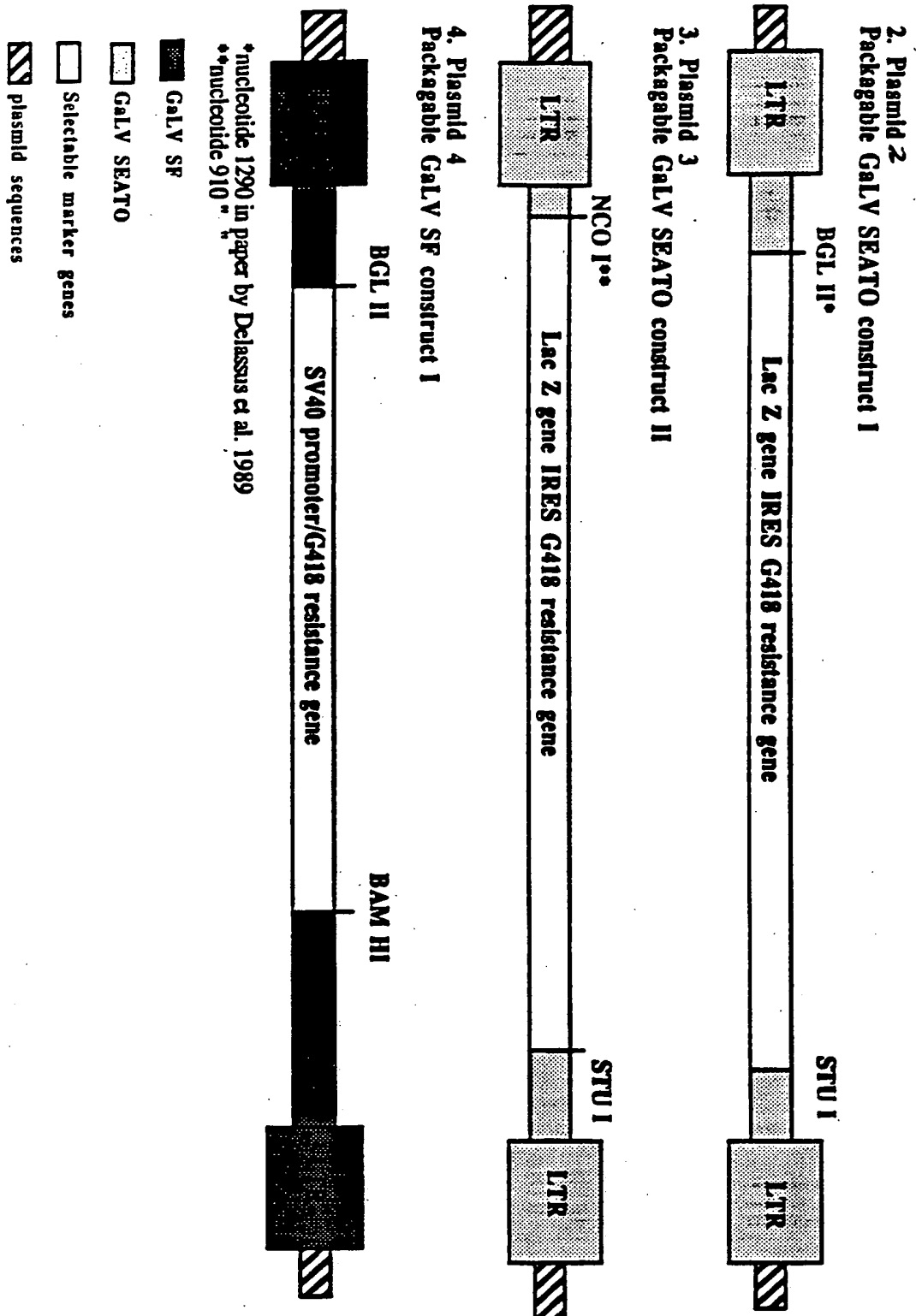
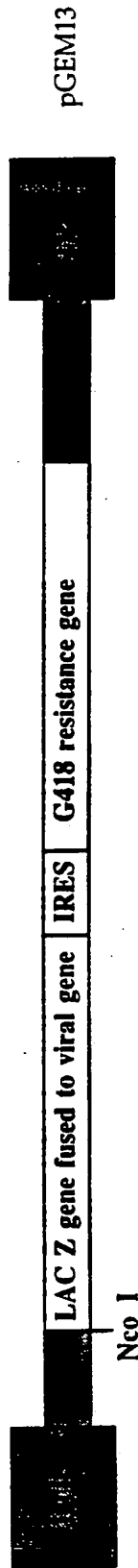


Figure 3

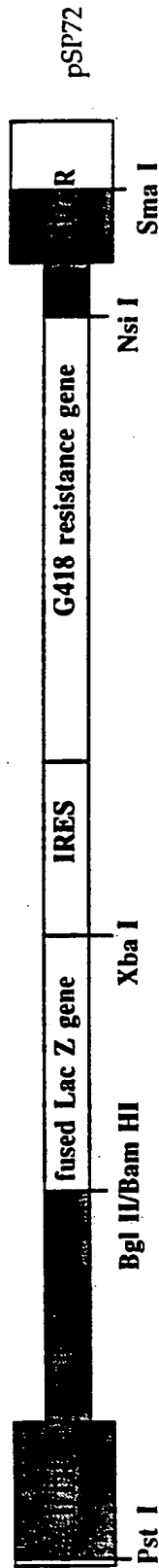
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GalV genomes

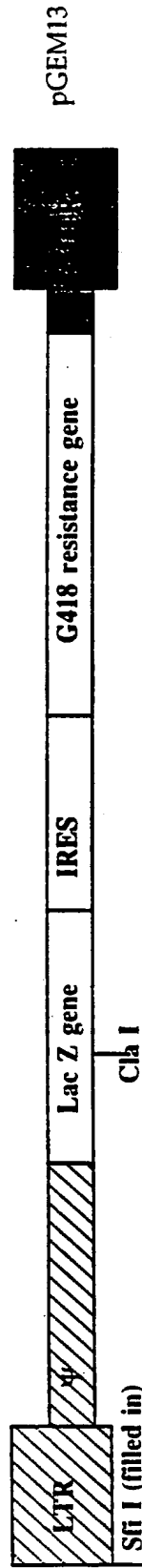
395



558



521



☐ GalV SF

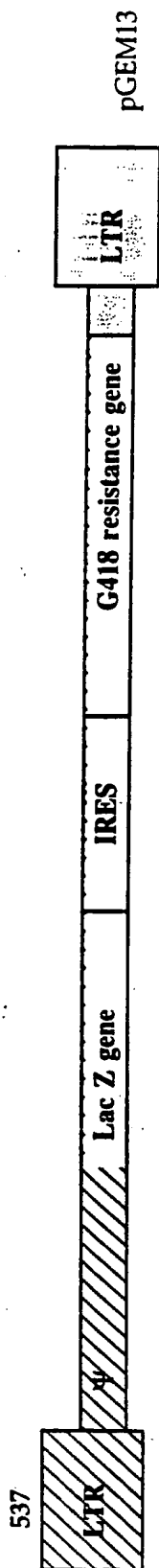
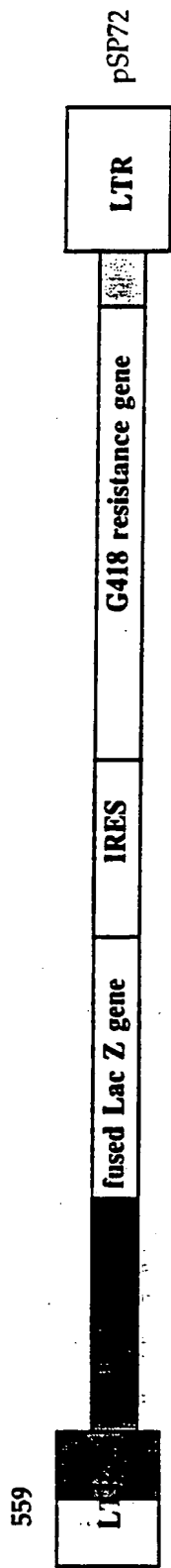
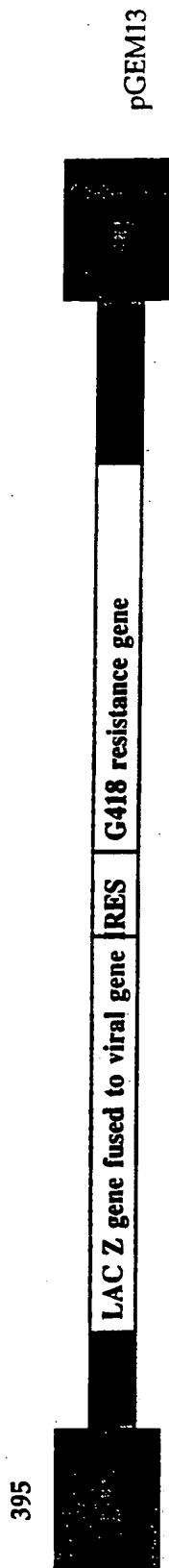
☒ GalV SEAT9

☒ MLV

☐ Selectable marker genes

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GaLV genomes



- ☐ GaLV SF
- ☒ GaLV SEATO
- ☒ MLV
- ☐ Selectable marker genes

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